DISSERTATION TITLED

"RELATIONSHIP BETWEEN THYROID FUNCTION AND ICU MORTALITY (SICK EUTHYROID SYNDROME)"

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CERTIFICATE

This is to certify that the dissertation entitled **"RELATIONSHIP BETWEEN THYROID FUNCTION AND ICU MORTALITY (SICK EUTHYROID SYNDROME)"** is a bonafide original work done by **DR. M. M. ARUN SHIVA RAMAN**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2013 - 2016.

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I solemnly declare that the dissertation entitled **"RELATIONSHIP BETWEEN THYROID FUNCTION AND ICU MORTALITY (SICK EUTHYROID SYNDROME)"** is done by me at Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 during 2015 under the guidance and supervision of Prof. K.S.CHENTHIL, M.D., to be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE BRANCH-I.

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ABBREVIATIONS

TFT	-	THYROID FUNCTION TEST
TBG	-	THYROGLOBULIN
TBPA	-	THYROID BINDING PREALBUMIN
CBC	-	COMPLETE BLOOD COUNT
ICU	-	INTENSIVE CARE UNIT
RFT	-	RENAL FUNCTION TEST
LFT	-	LIVER FUNCTION TEST
rT3	-	REVERSE T3
APACHE	-	ACUTE PHYSIOLOGICAL AND CHRONIC HEALTH EVALUATION
SOFA	-	SEQUENTIAL ORGAN FAILURE ASSESSMENT
SAPS	-	SIMPLIFIED ACUTE PHYSIOLOGICAL SCORE

CONTENTS

INTRODUCTION

INTRODUCTION

Nonthyroid illness syndrome or sick euthyroid syndrome refers to alterations that occur in thyroid hormone levels in response to any critical illness like sepsis, ARDS, patients on mechanical ventilation and also any ICU patients.

The metabolic response to any critical illness involves every organ but the underlying pathology is not completely understood. Despite the primary diagnosis, as a stress induced response in critical illness, a state of hypermetabolism prevails leading to increased energy expenditure, hyperglycemia and muscle loss.

Thyroid hormone alterations commonly occur in critical illness in patients with no previous known intrinsic thyroid disease. The changes in thyroid hormone levels is not an isolated phenomenon as it is also associated with changes in other endocrine axis as a response to stress.

Various theories have been proposed for alterations in thyroid function. In early course of the illness, the peripheral conversion of T 4 to T3 is reduced leading to decreased free T3 with normal or reduced T4 associated with an increase in reverseT3(rT3) and no alterations in TSH. In prolonged illness, central hypothyroidism occurs leading to reduced TSH and T4 along with T3.

In this study thyroid profile is taken from patients admitted in ICU on day 1 and day 7 and to correlate the levels the thyroid hormones and the outcome of the patients and also to know the outcome of the disease can be prognosticated with thyroid function tests in patients admitted in ICU.

AIMS & OBJECTIVES

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1) To study the relation between thyroid hormone level changes and critical illness in ICU patients.
2) To predict the mortality based on thyroid hormone levels in ICU patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

INTRODUCTION

Thyroid gland present in the neck produces two hormones namely triiodothyronine(T3) and thyroxine(T4). These hormones play a vital role in cell differentiation during development and maintains homeostasis including metabolic and thermogenic in adults.

ANATOMY

Thyroid gland(Greek *thyreos*, shield, and *eidos*, form)[1] is one of the most vascular organ weighs around 10 - 20 grams in adults.[2] Thyroid volume in men is greater than women which is measured by ultrasonography(USG).

It is a butterfly shaped organ present in middle of the neck. Thyroid gland extends just below cricoid cartilage and encircles trachea anterolaterally and extends just above suprasternal notch.

It consists of two lobes laterally and an isthmus which connects the two lobes. Isthmus is 0.5cm thick , 2cm high and 2cm wide. Each lobe is around 4cm in height and 2 – 2.5cm thick[3] and have a superior and inferior lobe. Pyramidal lobe, a finger like projection extends from isthmus just left to the midline. It is usually directed in an upward direction.

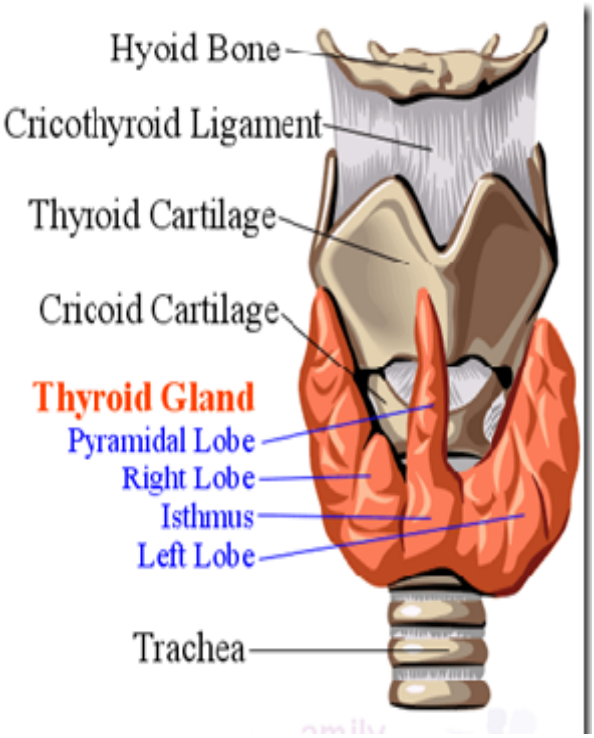


Figure 1 – Anatomy of thyroid gland

EMBRYOLOGY

Thyroid gland develops around 3rd week of intra uterine life. It is mainly derived from endoderm. The fourth pharyngeal pouch from its ventral portion develops into thyroid lobes.

Pyramidal lobe develops from thyroglossal duct as it descends and attaches itself to isthmus.

Ultimobranchial bodies, the neural crest cells arises from fourth and fifth brachial arches give rise to parafollicular C cells which synthesize calcitonin.

BLOOD SUPPLY

Thyroid is highly vascular and it has superior and inferior thyroid arteries which are present on both sides.

1) Superior thyroid artery- first branch of external carotid artery.
2) Inferior thyroid artery- arises from thyrocervical trunk which again is a branch of subclavian artery.
3) Thyroidea ima artery- in 3% population, branch of aortic arch.[4]

The average estimated blood flow to thyroid gland is around 4 – 6ml/min/gram of thyroid tissue.

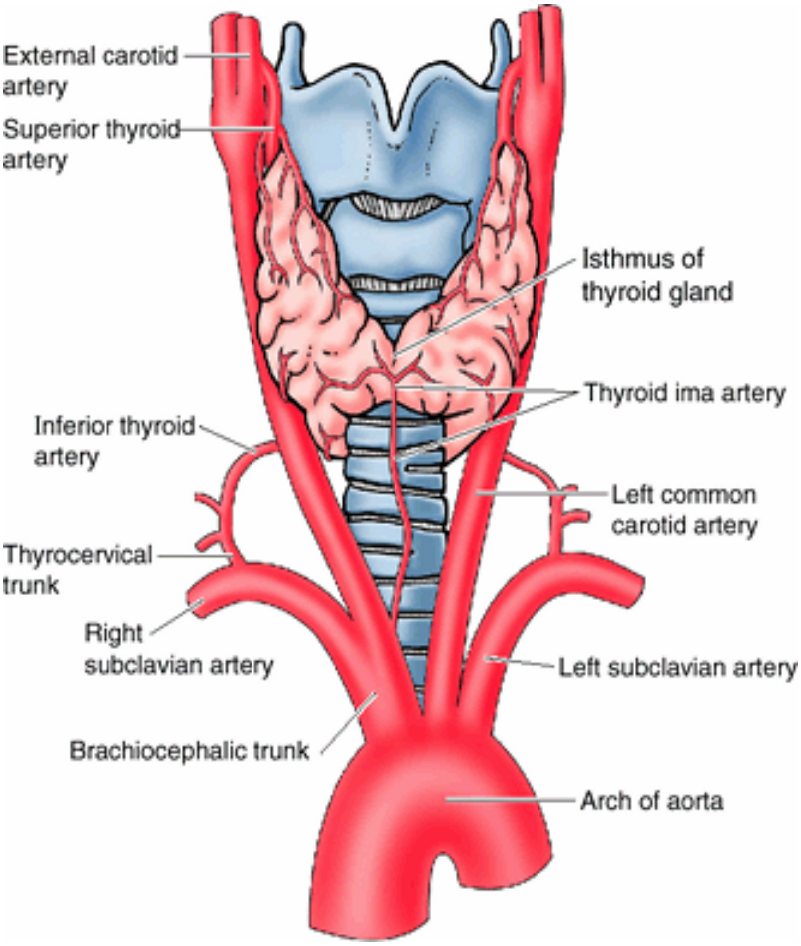


Figure 2 – Blood supply of thyroid gland

HISTOLOGY

Thyroid gland is composed follicles which are nothing but closely packed spherical units with rich capillary network. Follicles are filled with colloid (clear and proteinaceous). The diameter of follicle is around 200 µm. The height of follicle varies as it becomes columnar when it is active and cuboidal while inactive.[5]

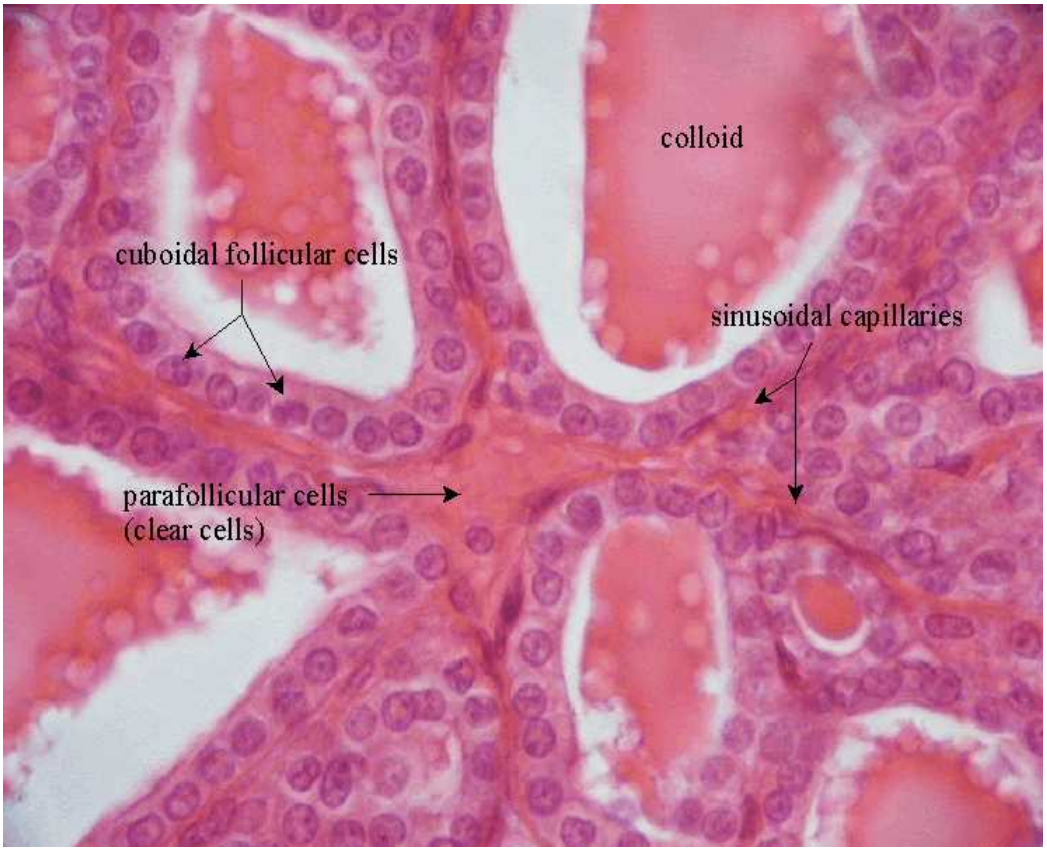


Figure 3 – Histology of thyroid gland

THYROID HORMONE SYNTHESIS AND SECRETION

Thyroid gland secretes T4 and T3. T4 levels predominate in secretion whereas T3 is more potent than T4. T4 gets converted to T3 in the peripheral tissues by deiodination.

Iodine forms the primary component in thyroid hormones. Dietary iodine gets absorbed from intestine and enters circulation. Minimum dietary intake required for maintain normal thyroid function is 150μg/day in adults. Normal uptake of iodine by thyroid gland is around 120μg/day in which around 80μg/day is secreted as thyroid hormone and remaining enters into circulation.

Iodine enters into thyrocytes through sodium/iodine symporter(NIS) present in the basolateral membrane of thyrocytes. This channel transports two sodium and one iodine ion into the cell.[6] This is a secondary active transport. NIS expression in the cell is mediated by thyroid stimulating hormone.

Iodine leaves the cell across the apical membrane to enter the colloid where thyroid hormone synthesis occurs, it leaves the cell via chloride/iodine exchanger (pendrin).

Iodine then undergoes organification at colloid thyrocyte interface. First it gets oxidized to form iodine and then gets incorporated into

thyroglobulin. Thyroglobulin in a glycoprotein synthesized by thyrocytes and leaves the cells to enter colloid by exocytosis. Thyroperoxidase which is present in apical membrane of thyrocytes mediates the oxidation and incorporation of iodine into thyroglobulin.[7]

Thyroid hormone synthesis involves a multistep process. First product formed is monoiodotyrosine (MIT) which is nothing ut thyroglobulin and oxidized iodine. Another molecule of iodine gets incorporated to form diiodotyrosine (DIT). Two molecules of DIT combine to form T4 by oxidation condensation reaction. T3 is formed when monoiodotyrosine condense with diiodotyrosine. When it occurs in a reverse manner (DIT + MIT) reverse T3 is synthesized.[8]

The daily secretion by thyroid gland consists of around 80 μg of T4, 4 μg of triiodothyronine and 2 μg of reverse T3 whereas DIT and MIT are not secreted. They are deiodinated by iodotyrosinase deiodinase which is present in microsomes. They recycle iodine which is utilized in the next cycle of thyroid hormone synthesis. T3 and T4 are resistant to deiodination by this enzyme and they appear in circulation.

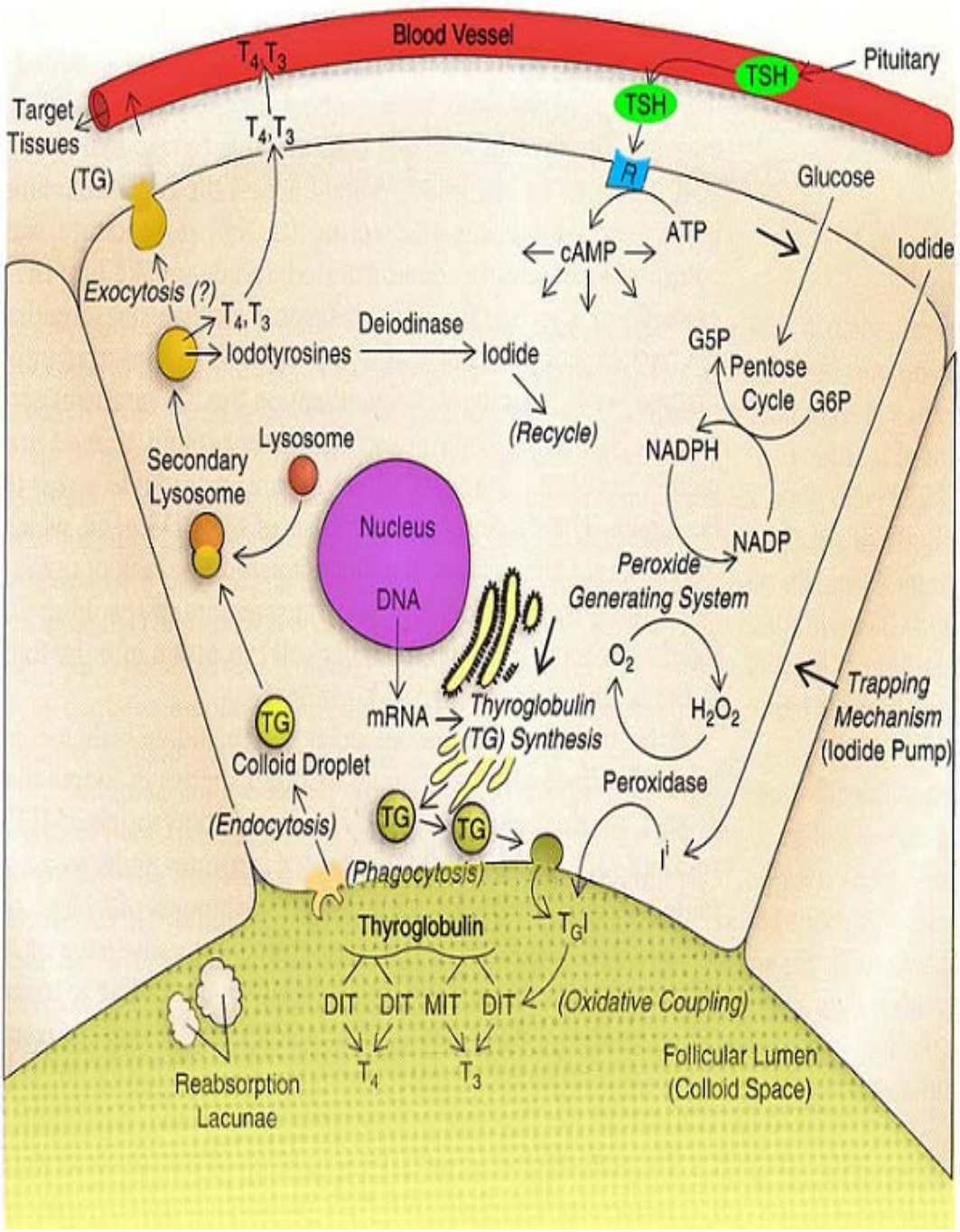


Figure 4 – Synthesis and secretion of thyroid hormone

THYROID HORMONE TRANSPORT

Thyroid hormones are present in circulation in free and protein bound form. T3 and T4 are lipophilic. Free and protein bound hormones are in equilibrium with one another. Free form is secreted by the gland. Free form is the active one and it mediates the action and feedback inhibition to pituitary gland and inhibiting the secretion of TSH.

The importance of protein binding is that the protein bound form maintains the large pool of hormones which are utilized readily when needed.[9]

Thyroid hormones are bound to three proteins namely albumin, transthyretin (prealbumin) and thyroxine binding globulin(TBG).[10] Of these albumin has the largest capacity and TBG has the least capacity to bind to the hormones. However in regard to the affinity of binding most of the hormones are bound to TBG. The half life of albumin is 13 days, TBG is around 5 days and that of transthyretin is 3 days.

T4 is more bound to T3 in plasma. This explains the longer half life of T4 when compared to T3. The half life of T4 is around 6-7 days. Since T3 is less protein bound it has faster onset of action than T4 at the level of tissues.

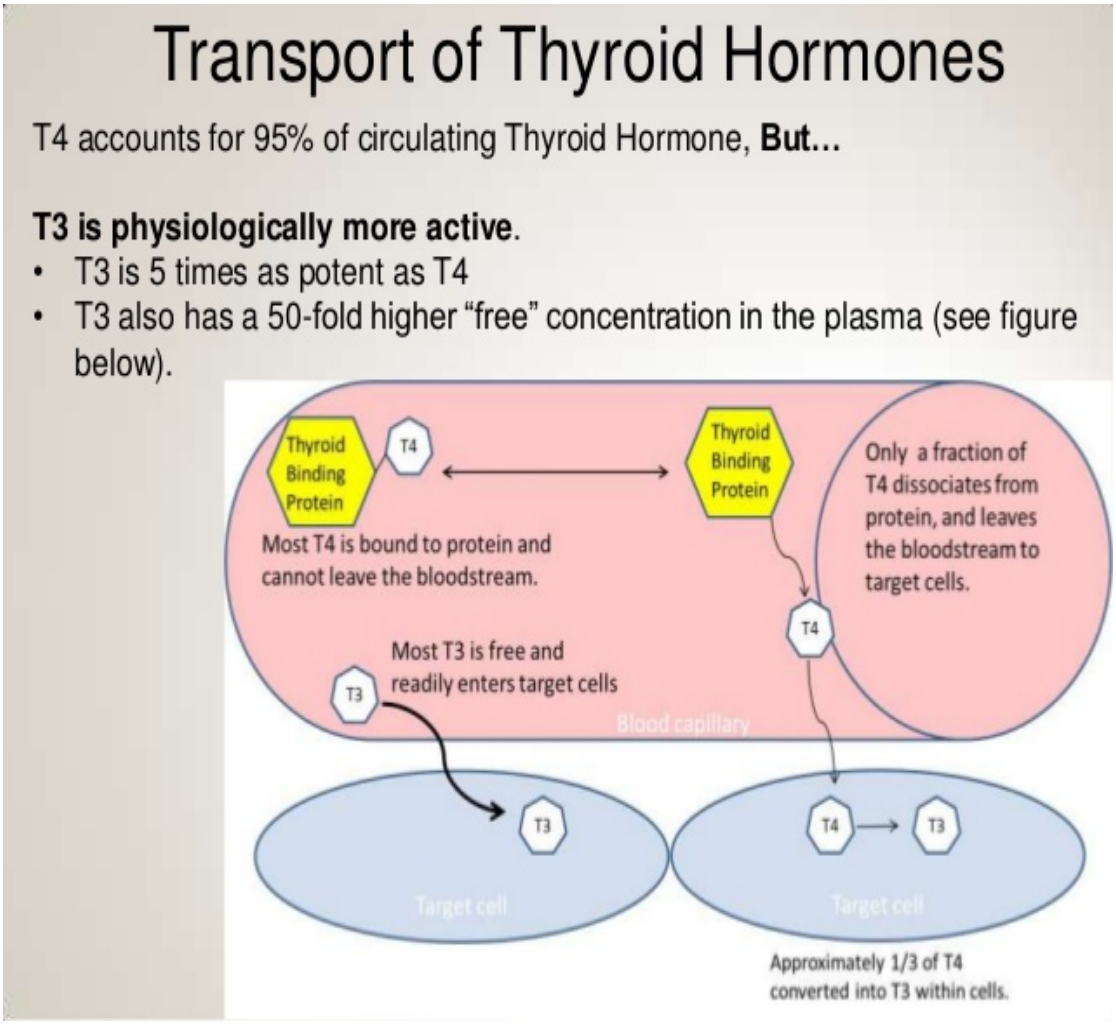


Figure 5 – Transport of thyroid hormones

METABOLISM OF THYROID HORMONE

Thyroid hormones are deiodinated principally in the liver, kidney and many other tissues. The importance of deiodination is that in addition to catabolism of the hormones it also helps in peripheral synthesis of T3 is the primary mediator of thyroid hormone actions at the level of tissues.

Only around 13% of circulating T3 is secreted by thyroid whereas the remaining 87% are synthesized by peripheral deiodination. Cerebral cortex and pituitary have high T3/T4 ratio due to the expression of deiodinases.[11]

There are three deiodinases present in the body D1, D2, and D3. D1 is seen in liver, pituitary, thyroid and kidneys. It mainly involves in the peripheral conversion of T4 to T3.[12] D2 is seen in brain, brown fat and pituitary. In brain it is present in astroglia and responsible for supply of T3 in brain.

D3 is presnt in reproductive tissues and brain and mainy involves in the synthesis of RT3. They are conjugated to sulfates and glucoronides in liver and secreted through bile and some enter enterohepatic circulation and rest are excreted in stools.

REGULATION OF THYROID SECRETION

Thyroid function is regulated by TSH secreted from anterior pituitary gland. TSH secretion is regulated by TRH secreted from hypothalamus. The

negative feedback inhibition for TSH secretion is mediated by T4 and T3. TSH is also inhibited during periods of stress.

TSH is a glycoprotein containing 211 aminoacids having two subunits α and β and they are encoded in chromosome 6 and 1 respectively. Both subunits are noncovalently linked with each other. TSH α is similar to FSH, LH, hCG α. β subunit mediates the function of TSH.

The half life of TSH is around 60 min. TSH is metabolized mainly in kidneys and to some extent in the liver. TSH secretion is diurnally variable. The secretion peaks at midnight and declines during the day. Since α subunit of hCG is similar to TSH it can activate thyroid receptors in large concentrations.

TSH receptors are G protein coupled receptors which acts via phospholipase C. T3 and T4 inhibit the secretion of TSH and TRH.[13]

OTHERS FACTORS AFFECTING THYROID GROWTH

Thyroid gland expresses IGF-1, EGF promote growth of the gland whereas INF γ and TNF inhibit the growth.

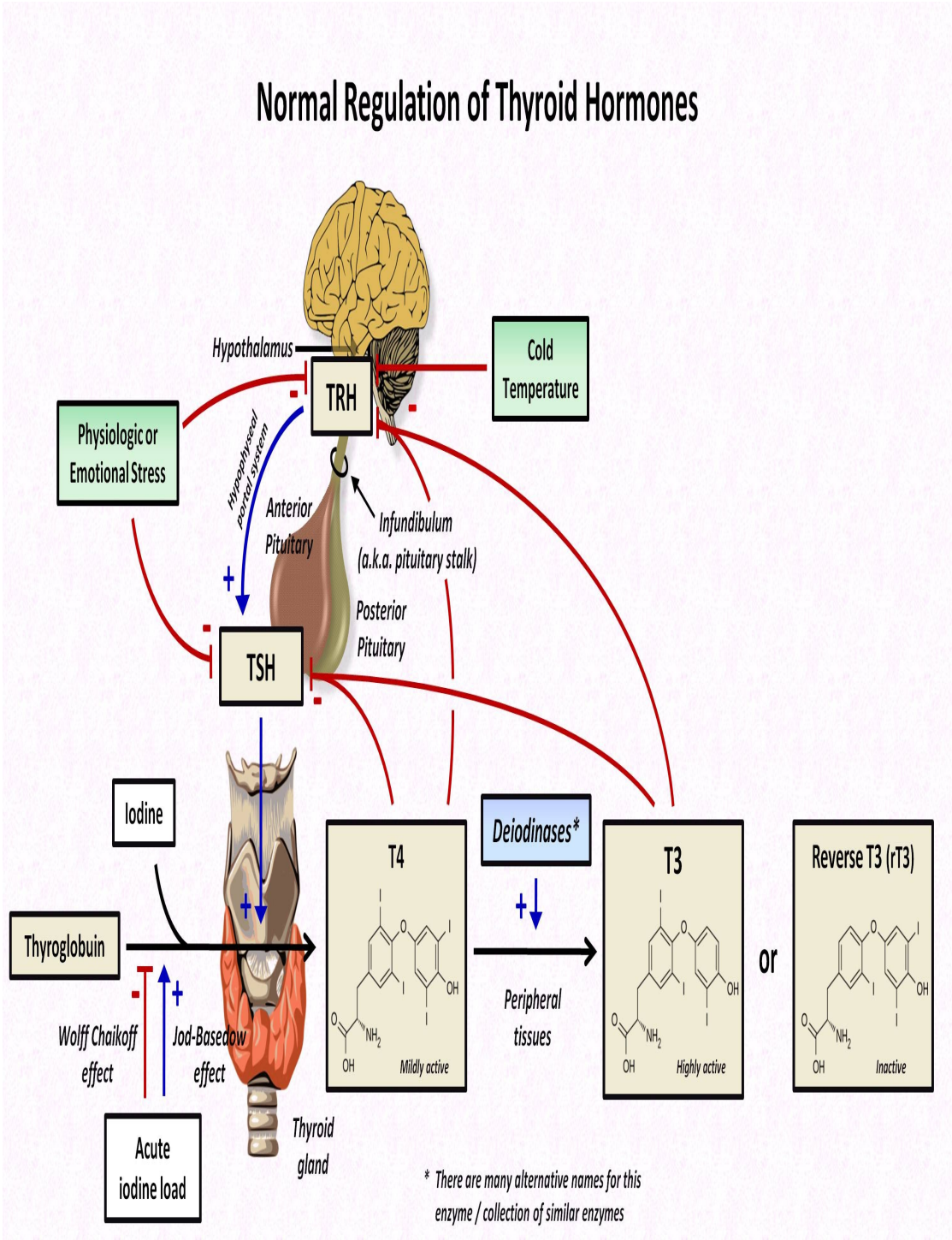


Figure 6 – Regulation of thyroid hormones

MECHANISM OF ACTION OF THYROID HORMONES

Thyroid hormones enter the cells and bind to thyroid receptors in the nuclei which then with the help of zinc fingers bind to DNA and mediates the function by expressing various genes which codes for protein and mediates various functions.

T3 is around five times more potent than T4. RT3 does not mediate any functions.

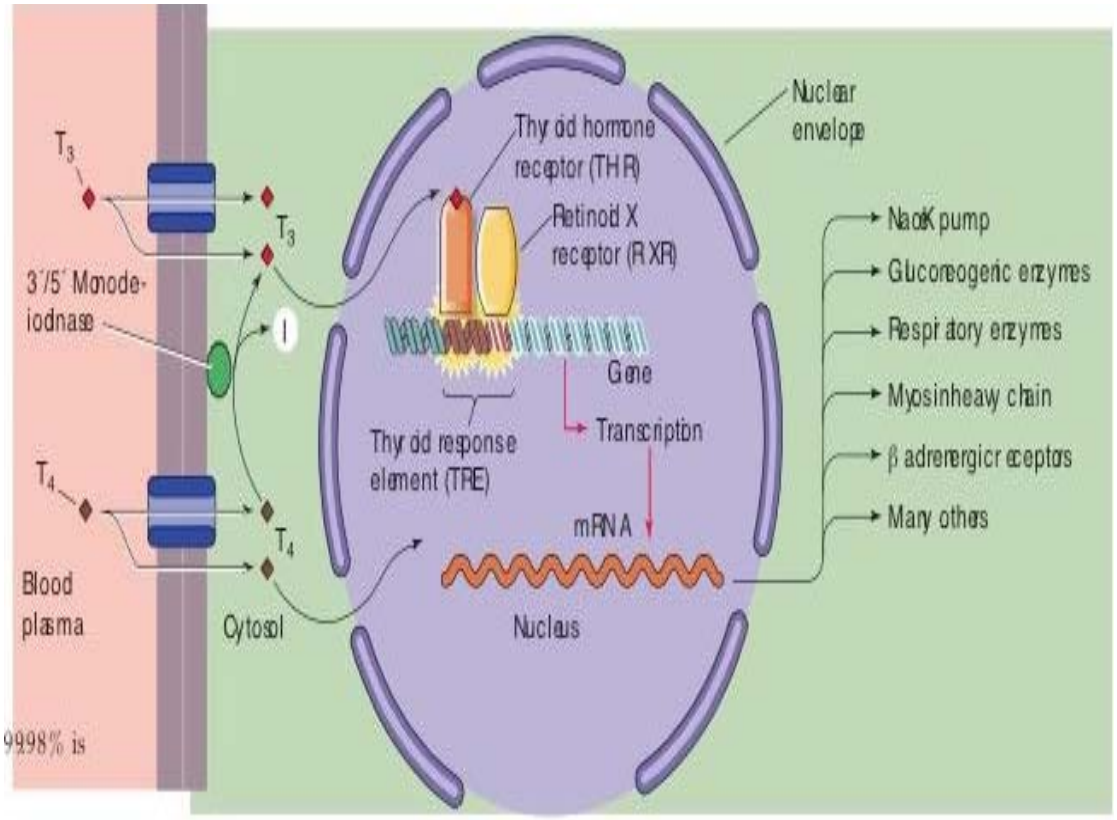


Figure 7 – Metabolism of thyroid hormones

PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

Table 1 – Functions of thyroid hormones

Target Tissue	Effect	Mechanism
Heart	Chronotropic and Inotropic	Increased number of β-adrenergic receptors Enhanced responses to circulating catecholamines Increased proportion of α-myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulated lipolysis
Muscle	Catabolic	Increased protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increased rate of carbohydrate absorption
Lipoprotein	Metabolic	Formation of LDL receptors
Other	Calorigenic	Stimulated oxygen consumption by metabolically active tissues (exceptions: testes, uterus, lymph nodes, spleen, anterior pituitary) Increased metabolic rate

LABORATORY MEASUREMENT OF THYROID FUNCTION

We use the following tests to assess thyroid function.

1. Thyroid stimulating hormone(TSH)
2. Serum total T4
3. Serum total T3
4. Serum free T3/ T4

Serum TSH measurement: Normal TSH levels range from 0.4-5mU/L. Second generation TSH immunometric assays can measure even upto 0.1mU/L.[14] TSH measurement is primarily useful in differentiating between hyperthyroidism from hypothyroidism and euthyroidism. But these assays cannot assess the degree of hyperthyroidism. Third generation assays can measure values <0.1mU/L and can be useful to assess the degree of hyperthyroidism.

TSH levels can also be used to initiate treatment in hypothyroidism. It also can used to follow up the patients and dosage adjustment.

Age related changes can occur with TSH values, it was illustrated in the National Health and Nutrition Examination Survey III (NHANES III). As per this survey, TSH concentrations were higher in older patients. For example around 70% of subjects have value around 4.5mU/L within the normal range.

Serum T3 and T4: They can be measured by chemiluminometric assay, radioimmunoassay or other immunometric assays. They measure both subgroups of hormones which are protein bound and free form. Normal total T4 values range from 4.6 to 11.2 mcg/dL. Total T3 values range from 75 to 195 ng/dL.

Serum free T3 and T4: Since bound hormone represents only the circulating pool and not the hormone which is readily available for cellular uptake and for nuclear receptor interaction assays to measure the free hormone levels are developed. During period of illnesses and intake of certain drugs can ater the protein binding of T3 and T4. This produces a disarray between free and total T3 and T4 levels. Free T4 can be measured by direct measurement, equilibrium dialysis, free hormone levels using thyroxine binding index and T3 resin uptake.

CLINICAL USES OF THYROID FUNCTION TESTS

1) Screening for thyroid dysfunction

Serum TSH measurement is the initial step in screening process. If TSH levels are elevated patients are screened for hyperthyroidism with serum free T3 are suband T4. If TSH leves are low patients are screened for hypothyroidism.

2) Monitoring drug levels during treatment

Patients with hypothyroidism who are taking levothyroxine, the adequacy of dosage can be monitored with serum TSH measurement. If TSH levels are elevated, L-thyroxine dosage has to increased.[15] If the levels are low dosage has to be lowered. Serum TSH is not a sensitive index in monitoring hypothyroidism.

Serum TSH can ony detect hyperthyroidism and not the degree of hyperthyroidism. Serum T3 levels are much more elevated the serum T4 in many patients. So serum T3 levels can be utilized to monitor patients with hyperthyroidism on treatment.

ANTITHYROID ANTIBODY

Antibodies directed against certain thyroid antigens can be measured in certain autoimmune conditions which may cause hypothyroidism or hyperthyroidism.

Antibody against thyroglobulin(Tg) – thyroglobulin is synthesized in follicular cells and secreted and stored as colloid.

Antibody against thyroperoxidase(TPO) – TPO is an enzyme that catalyzes the iodination of Tg and production of MIT and DIT.[16]

Almost all patients with hashimoto's thyroiditis have elevated antibodies against Tg and TPO.

Antibodies against TSH receptor can either stimulating, blocking or neutral. Stimulating antibodies are seen in grave's disease and blocking antibodies are seen in hashimoto's thyroiditis.[16]

HYPOTHYROIDISM

Hypothyroidism is commonly diagnosed in females (female : male ratio = 5-8 : 1). Prevalence of hypothyroidism in community based surveys is around 0.1 to 2 percent. The prevalence of subclinical hypothyroidism in adults is 4 – 10 percent.

Hypothyroidism can be :

1) Primary – intrinsic thyroid abnormality, pituitary and hypothalamic function are normal
2) Secondary - hypothyroidism due to pituitary problem leading to decreased TSH secretion
3) Tertiary – hypothyroidism due to hypothalamic disorder with insufficient TRH stimulation to pituitary gland.

SUBCLINICAL HYPOTHYROIDISM

This is an entity that can be described biochemically. Patients may be asymptomatic or can have only vague symptoms. Classically these patients have normal T4 and T3 concentrations with elevated TSH levels.[17]

CAUSES OF HYPOTHYROIDISM

Table 2 – Causes of hypothyroidism

PRIMARY DISEASE OF THYROID		
Congenital Agenesis Ectopic thyroid remnants	Autoimmune Atrophic thyroiditis Hashimoto's thyroiditis Postpartum thyroiditis	Defects of hormone synthesis Iodine deficiency Dyshormonogenesis Antithyroid drugs Other drugs (e.g. lithium, amiodarone, interferon
Infective Post-subacute thyroiditis Post-surgery Post-irradiation Radioactive iodine therapy External neck irradiation	Infiltration Tumour	
SECONDARY (TO HYPOTHALAMIC-PITUITARY DISEASE)	Hypopituitarism	Isolated TSH deficiency

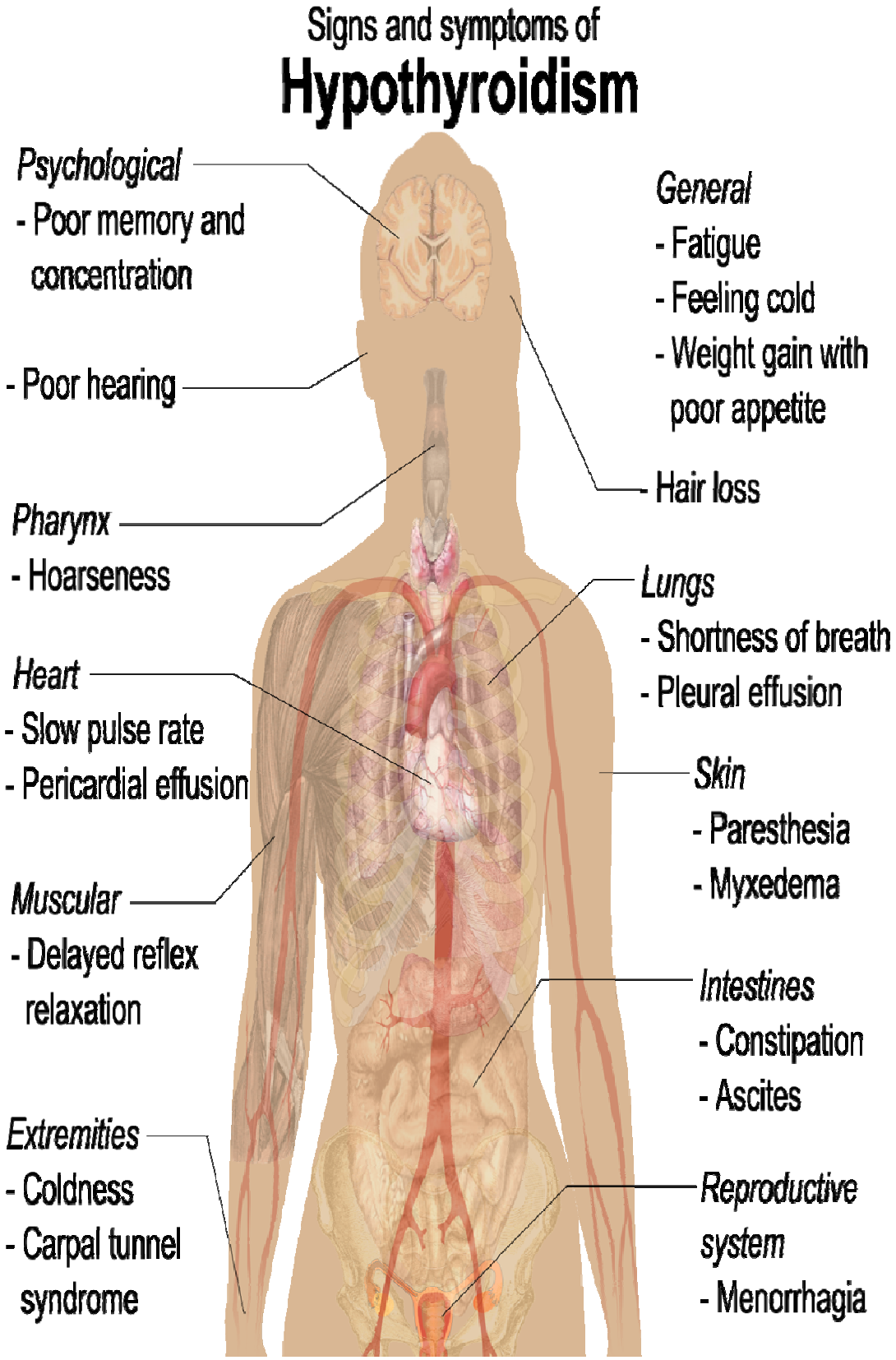


Figure 8 – Signs and symptoms of hypothyroidism

LABORATARY VALUES IN HYPOTHYROIDISM

Table 3 – Lab values in hypothyroidism

Type	TSH level	Free T_4 level
Primary hypothyroidism	Elevated	Low
Subclinical hypothyroidism	Elevated	Normal
Secondary hypothyroidism	Normal or low	Low

TSH, thyroid-stimulating hormone; T_4, thyroxine.

MANAGEMENT – AN OVERVIEW

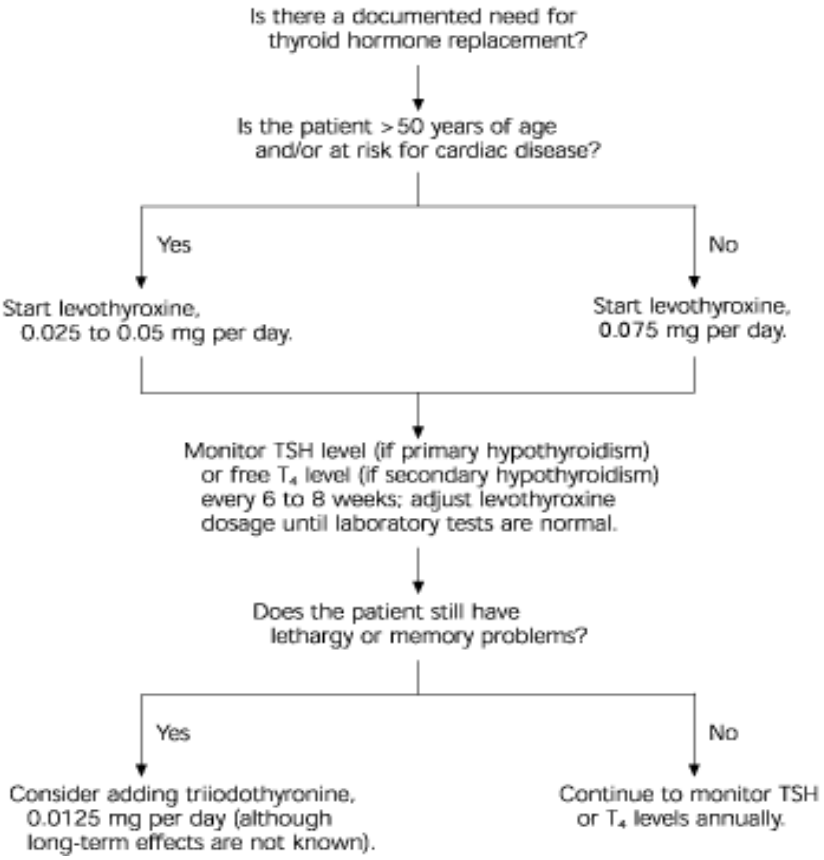


Figure 9 – Management algorithm for hypothyroidism

HYPERTHYROIDISM

Hyperthyroidism is a disease with constellation of symptoms due to excessive production of thyroid hormones by thyroid gland (hyperthreosis). Thyrotoxicosis is due to presence of increased thyroid hormones of any cause, one of which is hyperthyroidism.

CAUSES OF HYPERTHYROIDISM

Table 4 – Causes of hyperthyroidism

Most Common Causes	Rare Causes
• Graves' disease • Toxic multinodular goiter (also known as *toxic nodular struma*) • Independent or solitary toxic adenoma • Thyroiditis or inflammation of the thyroid gland	• TSH-secreting pituitary adenoma • Struma ovarii or goiter of the ovary (predominance or entire presence of matured thyroid cells in the ovary) • Metastatic differentiated thyroid cancer • Metastatic tumors within the thyroid gland

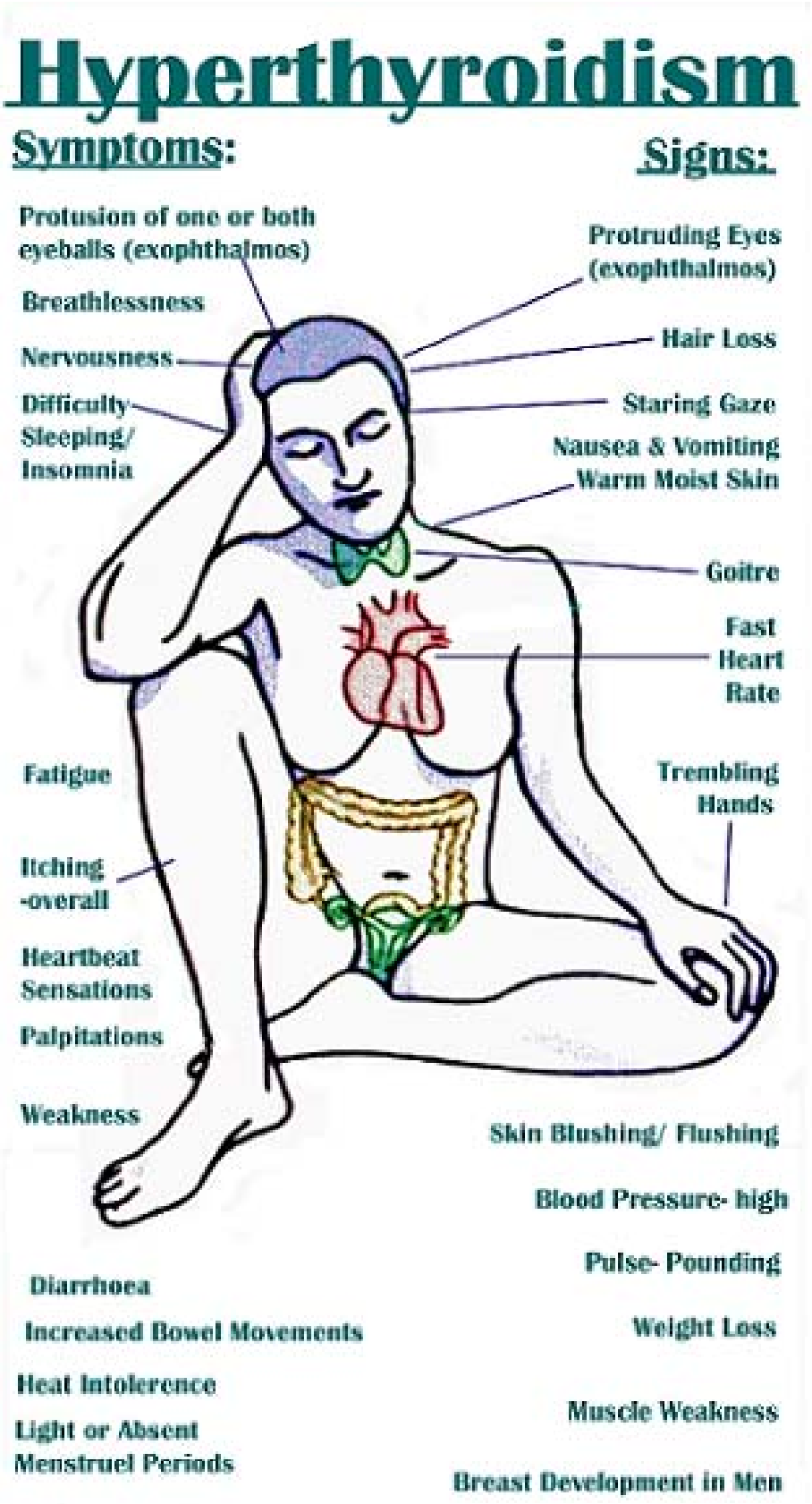


Figure 10 – Signs and symptoms of hyperthyroidism

INVESTIGATION

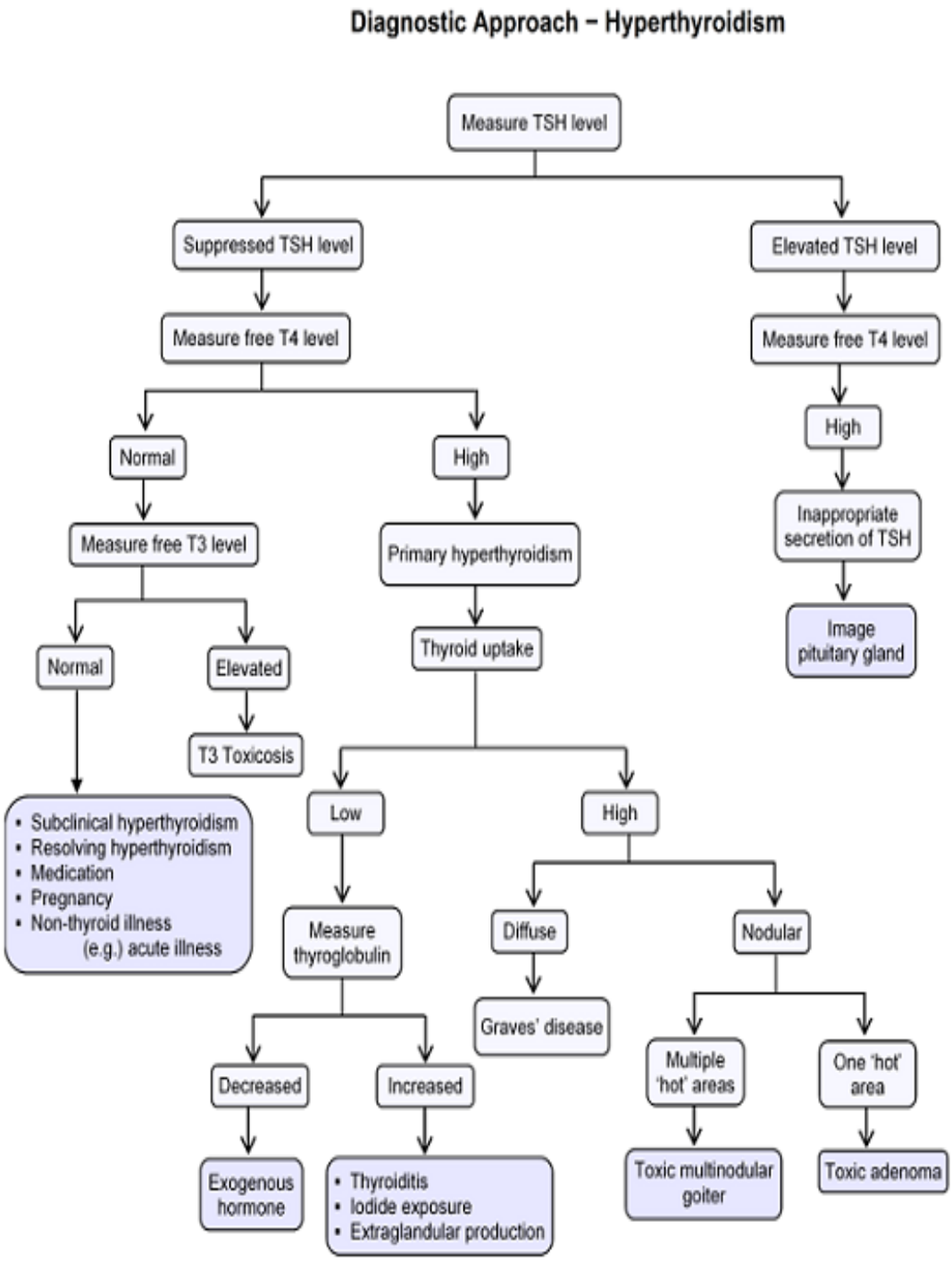


Figure 11 – Approach to hyperthyroidism

OVERVIEW OF MANAGEMENT

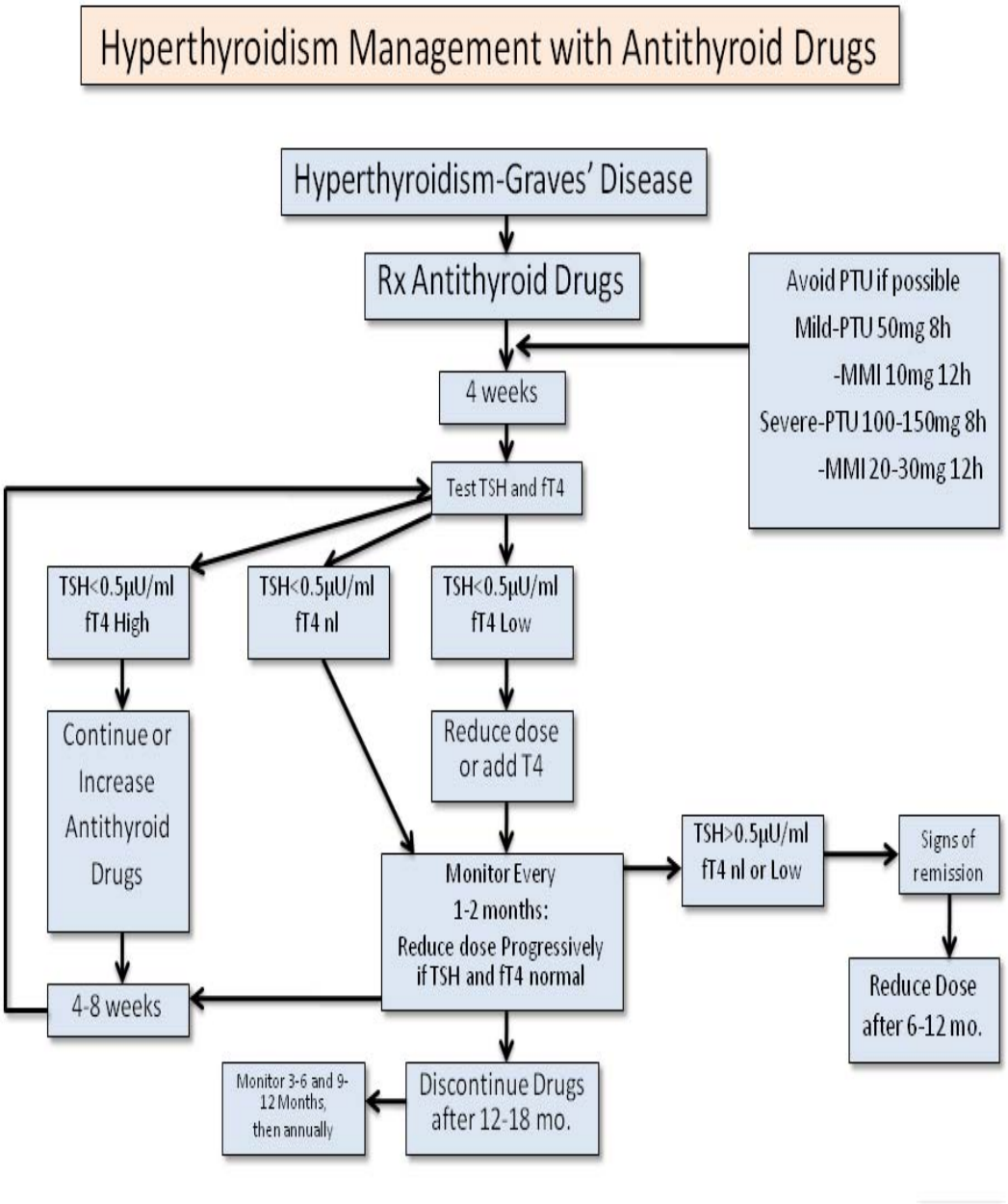


Figure 12 – Management overview for hyperthyroidism

THYROID FUNCTION IN CRITICAL ILLNESS

This entity in relation to thyroid function is also known as sick euthyroid syndrome, low T3 syndrome or nonthyroid illness syndrome. In any crictical illness, there is increased usage of energy, a hypercatabolic state leading to muscle loss.[18] In these states there are alterations in thyroid hormone levels in a previous euthyroxinemic leading to sick euthyroid syndrome. Alterations in thyroid function is a common phenomenon. But these changes are never an isolated phenomenon and associated with changes in other endocinological abnormalities.

Other endocrine changes include increased levels of adrenocorticotrophic hormone(ACTH) and serum cortisol levels. Decreased levels of gonadotrophin and sex hormone levels are also seen. So sick euthyroid syndrome should not be viewed as an isolated phenomenon but as a constellation of endocrine abnormalities seen in any critical illness.[19]

In order to understand and interpret the thyroid function tests one should know the normal physiological changes occurring in hypothalamic-pituitary-thyroid axis and thyroid hormone metabolism and effects of drugs on thyroid hormone metabolism.

T3 IN CRITICAL ILLNESS

The physiologically active component of thyroid hormones is T3. T3 levels are reduced in critical illness implies changes in thyroid hormone homeostasis and metabolism. Majority of T3 around 80% - 90% are being produced from peripheral monodeiodination of T4. This reaction is mediated by 5'- monodeiodinase, an enzyme present in liver, kidneys and aso other organs. The remaining 10% - 20% are being secreted by thyroid gland itself.

So inhibition of the enzyme 5'-deiodinase hampers the peripheral conversion of T4 to T3. Also many drugs used in ICU like amiodarone, corticosteroids and iodine inhibits the peripheral conversion.[20]

Majority of patients in ICU have low levels of T3. Liver biopsies taken within minutes after death in patients admitted in ICU showed that there is decreased concentration and activity of 5'- deiodinase. It also demonstrated that the activity of enzyme 5'- monodeiodinase. This enzyme is involved in synthesizing reverseT3(rT3). Also some patients with fatal illness reduced tissue levels of T4 and T3.

A number of mechanisms have been proposed that are involved in decreased activity of 5'- deiodinase. The reasons may be due to any one of the following:

1) Treatment with glucocorticoids
2) Cytokines (tumor necrosis factor alpha, interferon alpha, interleukin-6 and NF-kB) released in periods of stress.[21]
3) Non – esterified fatty acids which are circulating inhibitiors of deioinase activity.
4) Administration of drugs that inhibit the peripheral conversion of T4 to T3 like propronalol and amiodarone.

REVERSE TRIIODOTHYRONINE(rT3)

The rise in rT3 values along with the fall in T3 hormone levels are one of the most common findings observed in patients with critical illness.

The pathway involves the synthesis of rT3 catalyzed by 5'-deiodinase is called inactivating pathway. Since the activity of 5'-monodeiodinase activity is also reduced in critical illness, the conversion of rT3 to diiodothyronine is reduced. This pathway also contributes to increased levels of rT3 levels in patients with critical illnesses.

THYROXINE (T4)

Within 1 to 2 days of critical illness serum T4 levels can be reduced. Many mechanisms have been proposed which include reduced levels of thyroxine binding proteins like albumin, thyroid binding prealbumin and thyroid hormone binding globulin(TBG). Drugs like carbamazepine, aspirin,

phenytoin preferentially binds to the binding proteins. These drugs thus compete with thyroid hormones in protein binding which results in increased levels of free T4 and low levels of total T4. This phenomenon is a transient.[22]

Other factors include the presence of circulating inhibitors which prevents T4 protein binding like fatty acids, abnormal iodine uptake and abnormal peripheral metabolism. Drugs like barbiturates accelerate the clearance of T4 resulting low levels.

FREE T4

Though total T4 levels are low, free T4 levels remain normal in critical illness unless the illness is severe and prolonged.

In prolonged critical illnesses there is suppression of hypothalamic – pituitary axis. This leads to decreased TSH levels and T4 synthesis is reduced. This decrease in free T4 indicates the severity and it can be used as a predictor of poor outcome.

THYROTROPHIN(TSH)

Normally TSH secretion is stable and controlled by thyroid hormones, neuropeptides and neurotransmitters. Under normal conditions, thyrotrophin stimulating hormone (TSH) is the main stimulating factor. The

effect of TSH is enhanced by catecholamines. The main inhibitors include dopamine and somatostatin.

In sick euthyroid syndrome, TSH levels are usually normal. It may be low in prolonged illnesses. Serum TSH assays can detect around 0.01mU/L.

During recovery period from critical illness there may be transient rise in TSH levels upto 20mU/L. Few of these patients with elevated TSH levels when evaluated later once they recovered from the illness found to have hypothyroidism.

As seen earlier, the initial changes in thyroid hormone homeostasis is due to peripheral changes such as impaired deiodination and decreased release of thyroid hormones from the gland. Later on it is due to centrally induced hypothyroidism. Postmortem examination in these patients showed that there is decreased follicular size in thyroid gland, decreased expression of TRH mRNA in paraventricular nucleus of hypothalamus.[23]

Clinically, low T3 and T4 in association with normal, near normal or low TSH suggests the development of central hypothyroidism. These alterations may be a self protective mechanism so that energy can be preserved. These alterations are usually transient and normalizes once the patient starts to recover. During this period initially TSH rise followed by normalization of T4 levels. The half life of TSH is in hours while that of T4

is in days. So T4 values lag behind TSH levels. If TFT done during this period and interpreted the values may simulate primary hypothyroidism.

ASSESSMENT OF THYROID FUNCTION IN ICU

The reduced activity of 5'- monodeiodinase is not recognized since measurement of serum T3 is not the initial step in thyroid function tests. So, in patients with low TSH levels measurement of serum T3 levels help to differentiate between hyperthyroidism and sick euthyroid syndrome. In earlier T3 levels are elevated where as in the later the levels are decreased.

In an ICU patient, the differential diagnosis for low T4 and T3 should also include hypothyroidism. Here the measurement of rT3 helps in differentiating nonthyroid illness and secondary hypothyroidism. In hypothyroidism rT3 levels are low. In sick euthyroid syndrome, rT3 levels are elevated.

To conclude in assessing thyroid function in ICU two things to remember include:

1) Unless there is a strong suspicion of thyroid dysfunction, thyroid function should not be assessed.
2) If there is a strong suspicion, TSH alone is not sufficient to say that patient is having thyroid dysfunction.[24]

THYROID HORMONE REPLACEMENT IN NONTHYROID ILLNESS

It is still a matter of debate whether the changes that occur during critical illness are due to a protective mechanism or a maladaptive mechanism during periods of stress.

If the changes are due to pathologic process treatment with thyroxine will improve the outcome. If it is due to an adaptive process then treatment may worsen the outcome. The presence of low T3 and T4 in patients with critical illness have worse prognosis.

Only few studies have been conducted regarding treatment with supplemental thyroxine in non thyroidal illness patients. Brent and Hershman conducted one of those studies involving the effect of thyroxine replacement in patients admitted in intensive care units.

Inclusion criteria for this study was patients with serum T4 levels of <5 µg/dL with previous normal thyroid function. Patients were administered levothyroxine or placebo intravenously.

The observed result was there no significant difference in mortality between study population and controls. In fact T4 supplementation was found to be harmful as it hindered the normalization of thyroid axis during recovery phase.

Since the peripheral conversion of T4 to T3 is significantly suppressed in critical illness, one can say that levothyroxine supplementation does not appear to be beneficial.[25]

Another factor to be noted is that hepatic deiodinase is a selenoprotein. Selenium deficiency commonly occurs in critical illness particularly in sepsis. Thus selenium supplementation may result in early normalization of T4 and rT3.

Becker et al done a study in burn patients by replacing liothyronine(T3). They also concluded that there is no benefit in mortality. The most reasonable option is not to treat sick euthyroid patients.

Thyroid function tests can be useful in predicting the outcome of the patients. Among all the parameters free T3 has more sensitivity in predicting the outcome when compared with T4 and TSH. the levels of rT3 found to elevated in sick euthyroid syndrome.

DRUGS CAUSING ALTERATIONS IN THYROID FUNCTION

1)HYPOTHYROIDISM

Table 5 – Drugs casing hypothyroidism and its mechanism

DRUGS	MECHANISM
LITHIUM AMINOGLUTETHIMIDE THALIDOMIDE THIONAMIDE IODINE AMIODARONE	INHIBIT THYROID HORMONE SYNTHESIS AND/OR REEASE
CHOLESTYRAMINE CHOLESTIPOL ALUMINIUM HYROXIDE CALCIUM CARBONATE SUCRALFATE OMEPRAZOLE FERROUS SULPHATE	INHIBITS ABSORPTION OF T4
INTERFERON ALPHA INTERLEUKIN 2	IMMUNE DYSREGULATION

DOPAMINE	SUPPRESSION OF TSH SECRETION
SUNITINIB	POSSIBLE DESTRUCTIVE THYROIDITS
BEXAROTENE	INCREASED T4 CLEARANCE AND YSH SUPPRESSION

2. DRUGS CAUSING HYPERTHYROIDISM

Table 6 – Drugs causing hyperthyroidism and its mechanisms

DRUGS	MECHANISM
IODINE AMIODARONE	STIMULATION OF TSH AND RELEASE
INTERLEUKIN ALPHA INTERFERON GAMMA	IMMUNE DYSREGULATION

DRUGS CAUSING ABNORMAL THYROID FUNCTION TESTS WITHOUT THYROID DYSFUNCTION

Table 7 – Drugs causing thyroid dysfunction

DRUGS	MECHANISM
ANDROGEN DANAZOL GLUCOCORTICOID NICOTINIC ACID L- ASPARAGINASE	LOW SERUM TBG
ESTROGEN TAMOXIFEN CLOFIBRATE 5- FLUROURACIL	HIGH SERUM TBG
SALICYATE HEPARIN FUROSEMIDE NSAIDs	DECREASED T4 BINDING TO TBG

PHENYTOIN CARBAMAZEPINE RIFAMPICIN PHENOBARBITOL	INCREASED T4 CLEARANCE
DOBUTAMINE GLUCOCORTICOID OCTREOTIDE	SUPPRESSION OF TSH SECRETION
AMIODARONE GLUCOCORTICOID PROPRANOLOL PROPYLTHIOURACIL CONTRAST AGENTS(IOPANIC ACID)	IMPAIRED CONVERSION OF T4 TO T3

SCORING SYSTEMS USED TO PREDICT ICU MORTALITY

The care for critically ill patients in ICU has advanced over past decades. The clinical knowledge of the care provider along with illness scoring systems, the outcome of patients can be predicted.

Scoring systems for ICU patients can be classified into scoring systems that are specific for organ system/ specific disease (eg.Glasgow coma scale) and non specific (generic) scoring systems that can be used for all patients irrespective of the diagnosis.

PURPOSES OF SCORING SYSTEMS

Five major uses of scoring systems include :

1) It can be useful in randomized control trials and investigations.
2) Quantifies the severity of illness and for resource allocation.
3) To compare the quality of care provided in different ICUs and in same ICU over a period of time.
4) To assess the prognosis of patients in ICU and helping family members in making decisions regarding ICU care.
5) To assess whether the patients are suitable for specific novel treatment. (APACHE II is used for prescribing drotregocin alpha)

TYPES OF ICU SCORING SYSYEMS

Figure 13 – Classification of ICU scoring systems

Specific

a. head injury - Glasgow coma score

b. burns - % + age ~ mortality

c. trauma - injury severity score (ISS)
trauma score

d. IHD - NYHA / AHA classification

e. pancreatitis - Ranson's scoring criteria

f. liver failure - Child's classification

1. Anatomical – e.g. Injury Severity Score

- Useful for trauma audits and research

2. Therapeutic – e.g. Therapeutic Intervention Scoring System (TISS)

- Sum of weighted scores of therapeutic interventions
- Correlates well with outcome
- Wide applicability

3. Physiological – e.g. APACHE – Acute physiology and chronic health evaluation

• Designed for quality review rather than prognosis

SPECIFIC MODELS

First generation - APACHE I

Second generation – APACHE II, SAPS I, MPM I

Third generation – APACHE III, SAPS II, MPM II

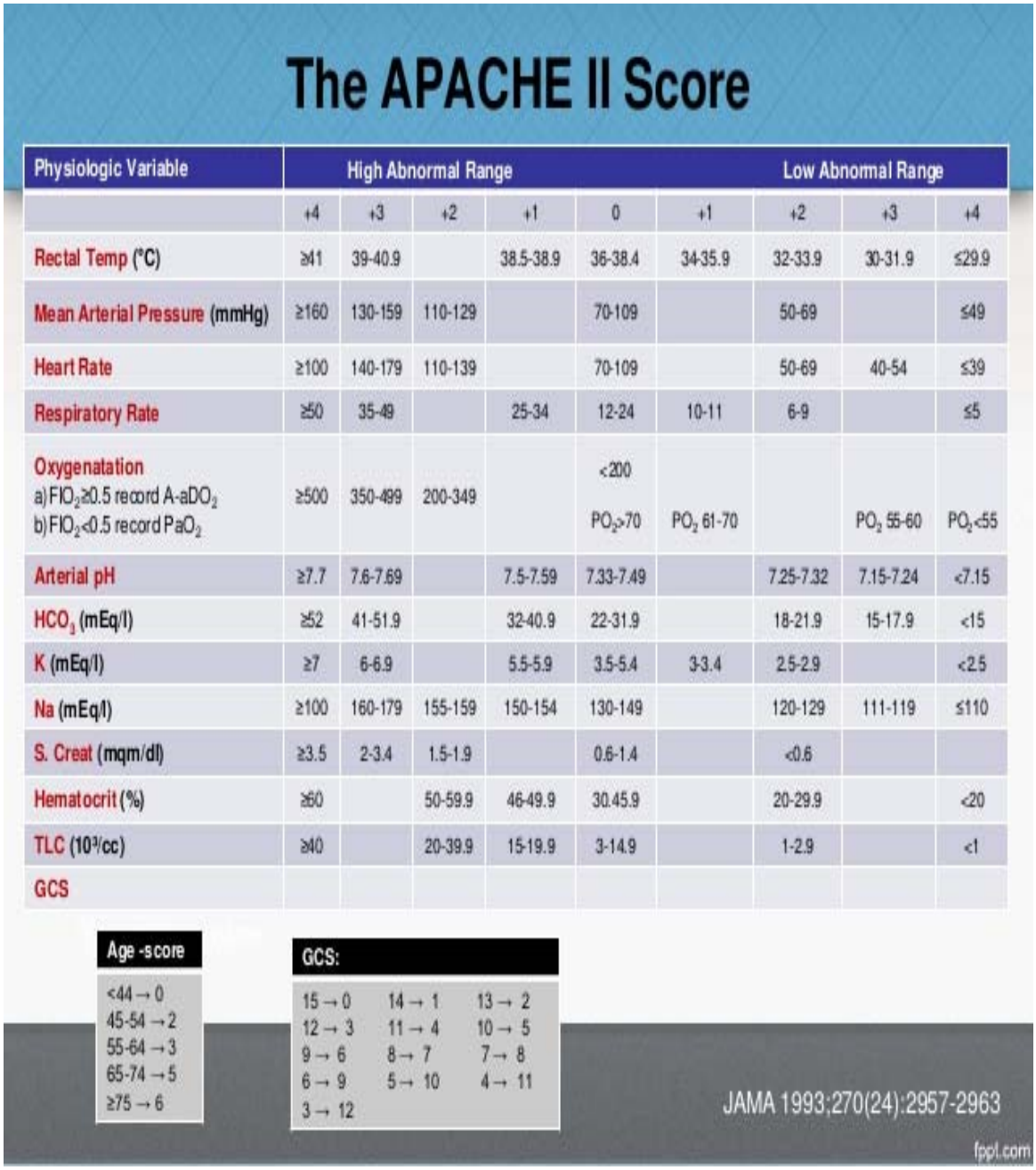
Fourth generation – APACHE IV, SAPS III, MPM III

ACUTE PHYSIOLOGICAL AND CHRONIC HEALTH EVALUATION SCORE (APACHE) II

In 1981, APACHE scoring system was initially developed to assess the severity in ICU patients. In 1985 William Knaus et al who were the aurthors of initial scoring system published APACHE II.[26] The advantage of APACHE II was that it can predict the mortality in ICU patients. It is still the most commonly used scoring systems to predict the outcome.

The scores range from 0 to 71 points. Physiological variables contribute around 60 points. Around 6 points for age and 5 points for previous health status.

Table 8 - APACHE II Score



The APACHE II Score

Physiologic Variable	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal Temp (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥100	140-179	110-139		70-109		50-69	40-54	≤39
Respiratory Rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation a) FIO_2≥0.5 record A-aDO_2 b) FIO_2<0.5 record PaO_2	≥500	350-499	200-349		<200 PO_2>70	PO_2 61-70		PO_2 55-60	PO_2<55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
HCO_3 (mEq/l)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
K (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Na (mEq/l)	≥100	160-179	155-159	150-154	130-149		120-129	111-119	≤110
S. Creat (mgm/dl)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30.45.9		20-29.9		<20
TLC (10^3/cc)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GCS									

Age -score

<44 → 0
45-54 → 2
55-64 → 3
65-74 → 5
≥75 → 6

GCS:

15 → 0 14 → 1 13 → 2
12 → 3 11 → 4 10 → 5
9 → 6 8 → 7 7 → 8
6 → 9 5 → 10 4 → 11
3 → 12

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APACHE III

This scoring system was developed in 1988-1989

APACHE III included acute physiological score (APS), age and chronic health status. It has scores from 0 to 299. 252 points for physiological variables, 24 for age and 23 for chronic health status.

The major limitation of this scoring system is the calculating software is very expensive one which makes it difficult to use APACHE III in all centres.

APACHE IV

It was devised in 2006. It is more complex as it has 142 variables. It is done and validated only in ICUs in USA.

SIMPLIFIED ACUTE PHYSIOLOGICAL SCORE(SAPS)

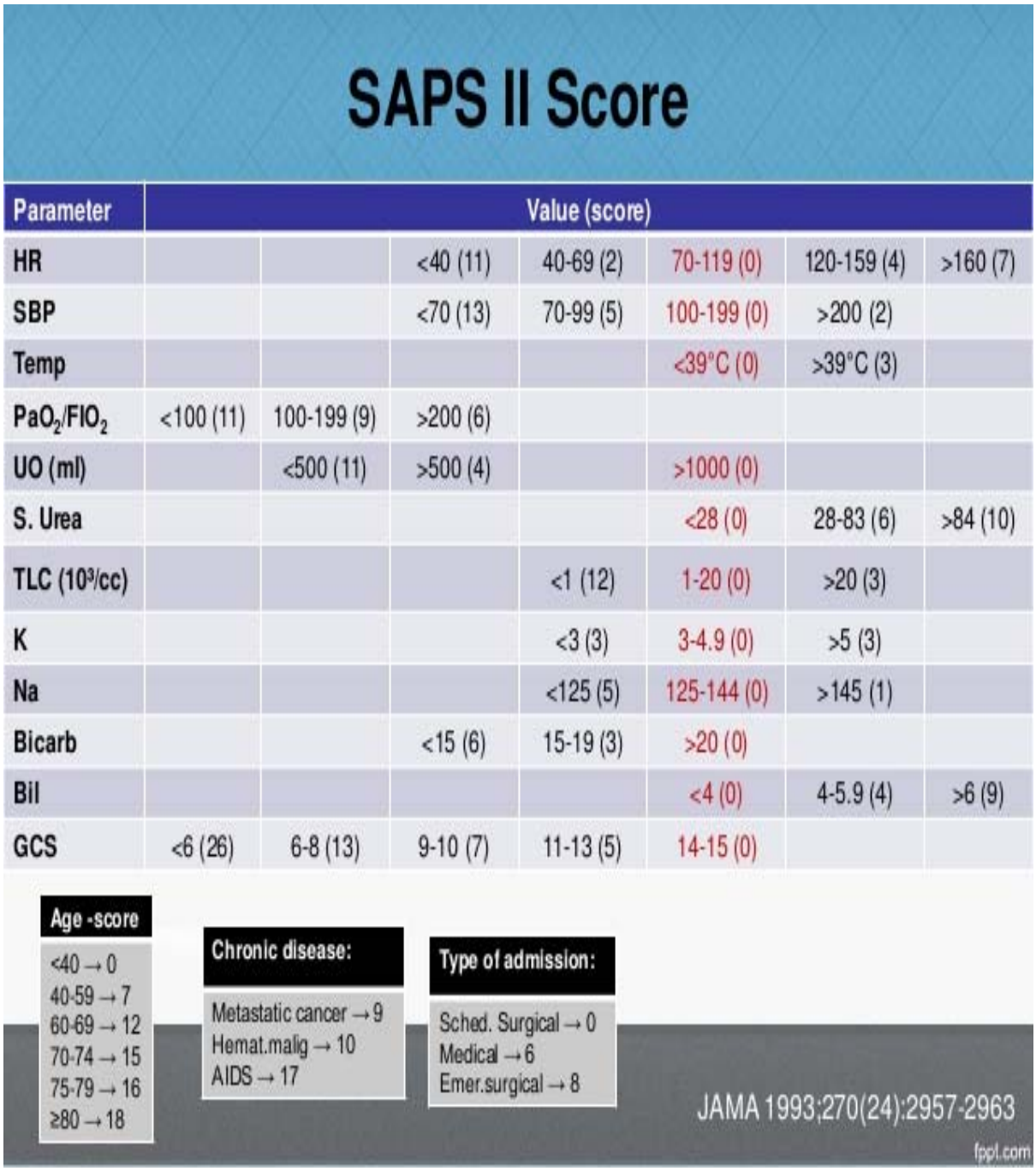
SAPS system of scoring came into practice in 1984. It used 13 variables and age in the scoring system. Like APACHE, SAPS scoring also done within 24 hours to predict the mortality.

SAPS II

Jean roger Le gall et al devised SAPS II in 1993. This score. SAPS II included 17 variables. The maximum score is 163 and the minimum is 0. It

is calculated within 24 hours of admission. The exclusion criteria included age <18 years, myocardial infarction, burns and cardiac surgery.

Table 9 – SAPS II Score



SAPS II Score

Parameter	Value (score)						
HR			<40 (11)	40-69 (2)	70-119 (0)	120-159 (4)	>160 (7)
SBP			<70 (13)	70-99 (5)	100-199 (0)	>200 (2)	
Temp					<39°C (0)	>39°C (3)	
PaO_2/FIO_2	<100 (11)	100-199 (9)	>200 (6)				
UO (ml)		<500 (11)	>500 (4)		>1000 (0)		
S. Urea					<28 (0)	28-83 (6)	>84 (10)
TLC (10^3/cc)				<1 (12)	1-20 (0)	>20 (3)	
K				<3 (3)	3-4.9 (0)	>5 (3)	
Na				<125 (5)	125-144 (0)	>145 (1)	
Bicarb			<15 (6)	15-19 (3)	>20 (0)		
Bil					<4 (0)	4-5.9 (4)	>6 (9)
GCS	<6 (26)	6-8 (13)	9-10 (7)	11-13 (5)	14-15 (0)		

Age -score
<40 → 0
40-59 → 7
60-69 → 12
70-74 → 15
75-79 → 16
≥80 → 18

Chronic disease:
Metastatic cancer → 9
Hemat.malig → 10
AIDS → 17

Type of admission:
Sched. Surgical → 0
Medical → 6
Emer.surgical → 8

JAMA 1993;270(24):2957-2963

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MORTALITY PREDICTION MODEL II

Mortality prediction model was devised in 1993. Researchers utilized the same variables and exclusion criteria used in SAPS II. This scoring system is calculated at the time of admission (MPM II0) and 24 hours after admission (MPM II24) for periction of mortality.

SEQUENTIAL ORGAN FAILURE ASSESSMENT(SOFA)

SOFA was initially developed in 1994 to describe organ dysfunction in patients with sepsis. Nowadays, it has since been validated to describe the degree of organ dysfunction in various ICU patient groups with organ dysfunctions not due to sepsis.[27]

The SOFA score involves six organ systems (respiratory, cardiovascular, renal, hepatic, central nervous, coagulation), and the function of each is scored from 0 (normal function) to 4 (most abnormal), giving a possible score of 0 to 24.Mortality rate increases as number of organs with dysfunction increases.

Table 10 – SOFA Scoring system

SOFA score	0	1	2	3	4
Respirationa PaO_2/FIO_2 (mm Hg) SaO_2/FIO_2	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine </=5 or dobutamine (any)	Dopamine >5 or norepinephrine </=0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

ICU STAY, THYROID PROFILE AND ICU SCORING SYSTEMS:

As discussed earlier, thyroid hormone assessment can be useful in predicting the mortality in ICU patients independently. The correlation of thyroid hormone assessment and ICU severity scores parallel with each other in predicting the mortality. Among the thyroid profile parameters free T3 has more sensitivity in predicting the outcome than T4 and TSH because T3 is the first hormone to be affected in sick euthyroid syndrome, since the main pathogenesis is the reduced peripheral conversion of T4 to T3.

MATERIALS

&

METHODS

MATERIALS AND METHODS

Study centre: Intensive care unit(ICU), Institute of internal medicine, Rajiv Gandhi government general hospital, Chennai-3

Study design: Prospective study

Sample size: 40 patients

Duration of study: 6 months

Inclusion criteria:

1. Patients admitted in ICU irrespective of the diagnosis.

2. Patients with ICU stay more than 7 days.

Exclusion criteria:

1. Patients with previous intrinsic thyroid, hypothalamic – pituitary axis disease.

2. Usage of iodine contrast agents in the past 8 weeks.

3. Usage of drugs causing hypothyroidism.

METHODOLOGY

Data collection and methods:

Patients eligible for the study are subjected to clinical examinations and investigations.

Methodology:

Patients admitted in ICU irrespective of their primary diagnosis are selected for this clinical study as per inclusion/exclusion criteria and are subjected to history taking and clinical examination after obtaining informed consent.

After clinical examination patients will be subjected for routine investigations like complete hemogram, renal function tests, liver function tests, arterial blood gas analysis, blood and urine culture and sensitivity(if needed). They are also subjected to thyroid function test on day 1 of their ICU stay.

All the patients in the study are followed up in ICU as they are getting treated and their status is monitored over a week. After 1 week time patients are again subjected to thyroid function tests

on day 7 of their ICU stay. Clinical progression over days is observed in terms of recovery from the illness or death of the patient. Finally thyroid function tests are analyzed whether they can predict the outcome of the patient by serial monitoring over 7 days.

Investigation details:

Serum thyroid profile

OBSERVATION

&

RESULTS

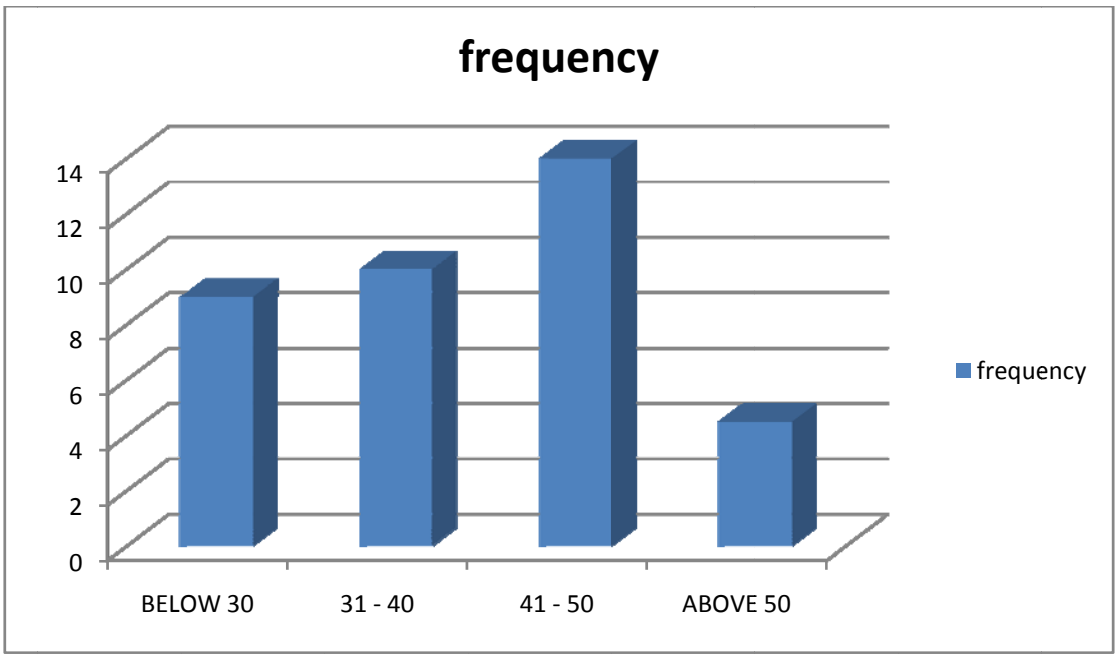
OBSERVATION & RESULTS

Table 11 -Age distribution

Age in years	Frequency	Percentage
Below 30	9	22.5
31-40	10	25.0
41-50	14	35.0
Above 50	7	17.5
Total	40	100.0

In our study, 14 out of 40 patients were in the age group between 41 – 50 years. But this is not statistically significant.

Figure 14 – Age distribution



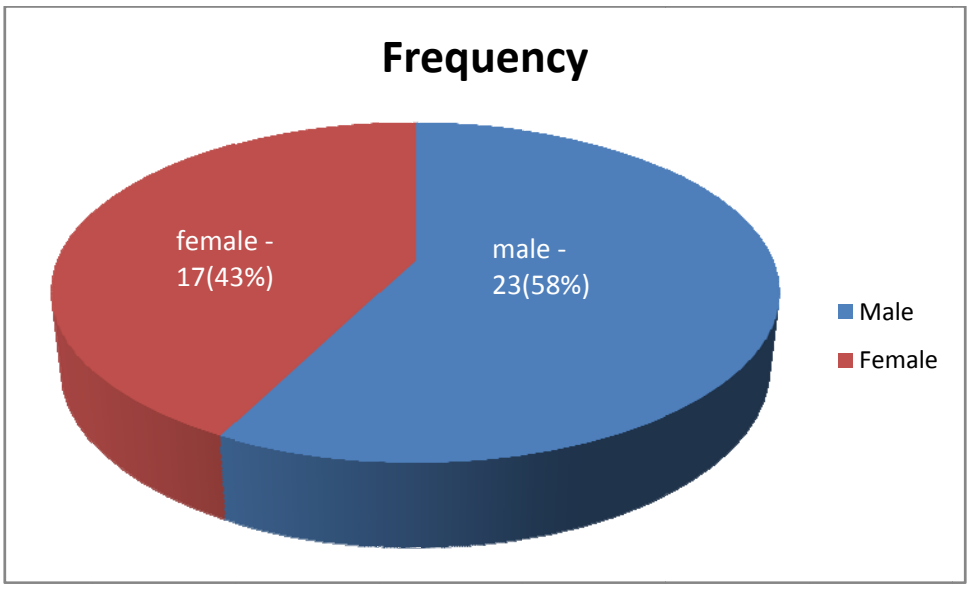
Sex distribution

Table 12 – sex distribution

sex	Frequency	Percent
Male	23	57.5
Female	17	42.5
Total	40	100.0

Among 40 patients, 23 were found to be males and 17 were found to be females.

Figure 15 – Sex distribution



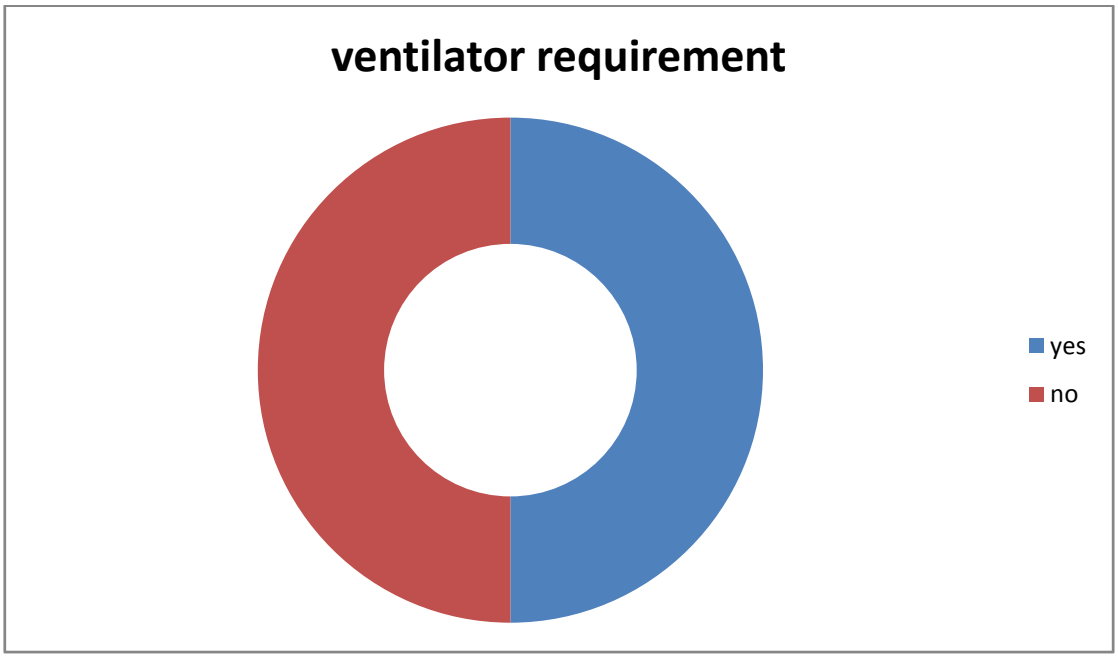
Ventilator requirement

Table 13 – patients requiring ventilator

ventilator	Frequency	Percent
Yes	20	50.0
No	20	50.0
Total	40	100.0

In our study, out of 40 patients 20 of them were on ventilator.

Figure 16 – Ventilator requirement



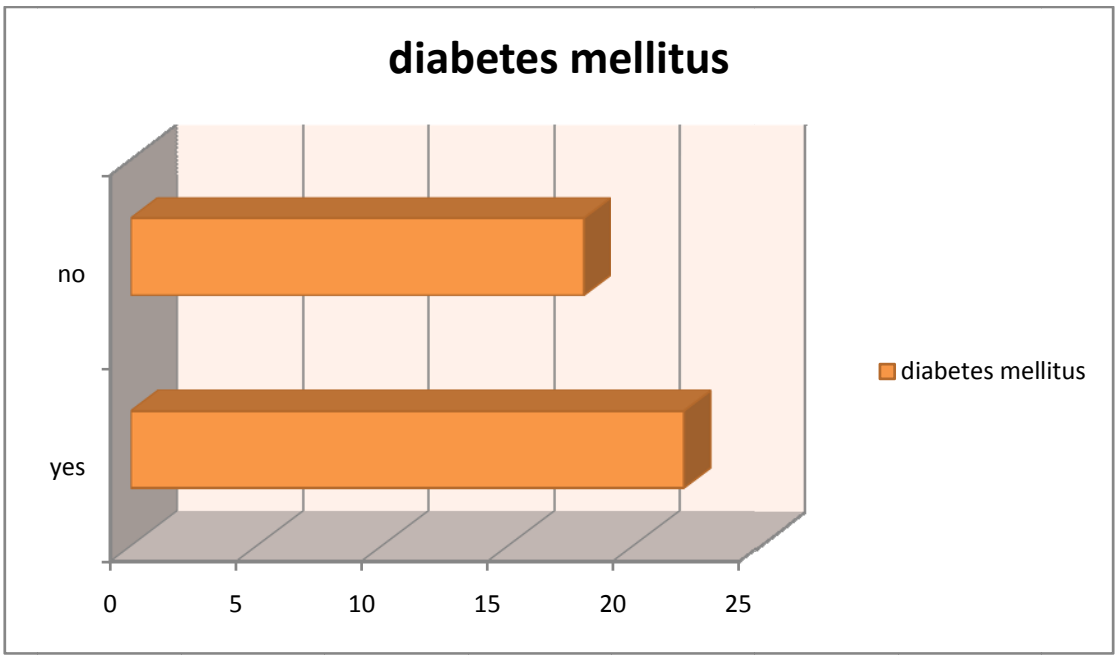
Diabetes mellitus

Table 14 – patients with diabetes mellitus

Diabetes mellitus	Frequency	Percent
Yes	22	55.0
No	18	45.0
Total	40	100.0

In our study, 22 out of 40 patients were having diabetes mellitus.

Figure 17 – Frequency of Diabetes mellitus



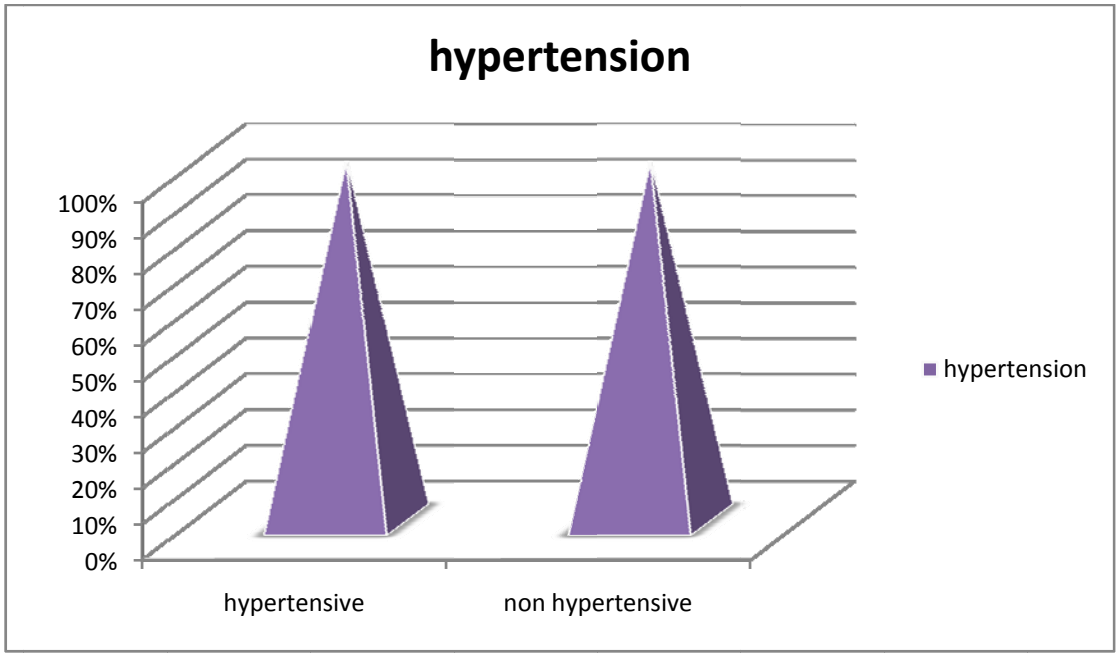
Number of patients with Hypertension

Table 15 – Patients having hypertension

Hypertension	Frequency	Percent
Yes	20	50.0
No	20	50.0
Total	40	100.0

In our study, out of 40 patients 20 were having hypertension and 20 were without hypertension

Figure 18 – Frequency of Hypertension



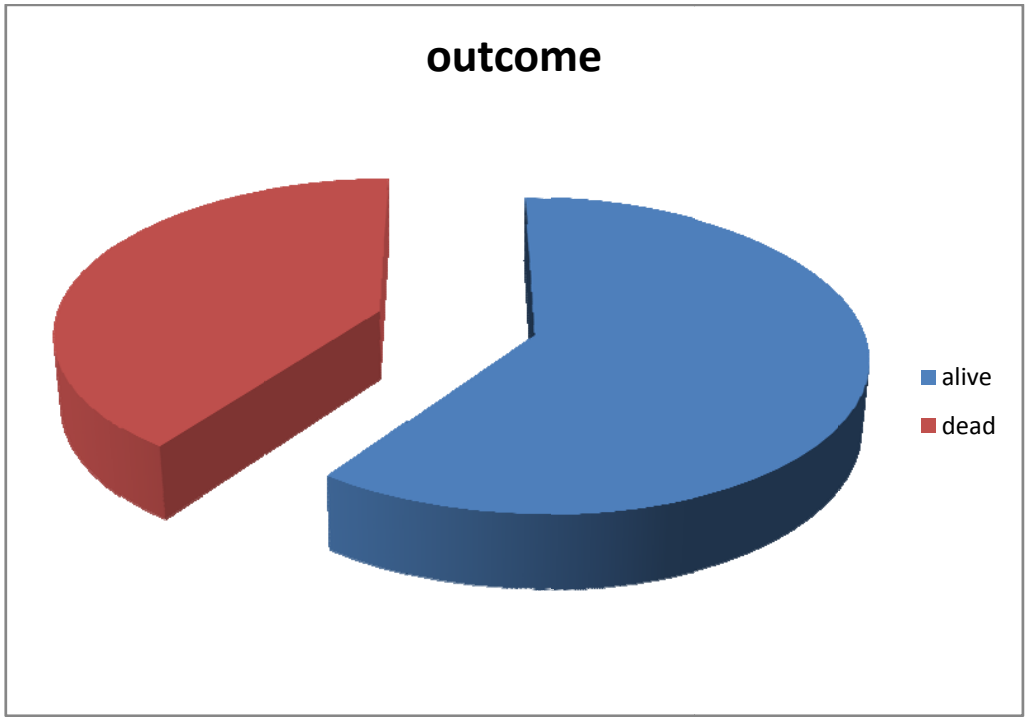
Outcome of Patients

Table 16 – outcome of patients

Outcome	Frequency	Percent
Alive	24	60.0
Dead	16	40.0
Total	40	100.0

In our study, 60% of patients were alive at the end point and were discharged. 40% patients were expired.

Figure 19 – Outcome of patients in the study



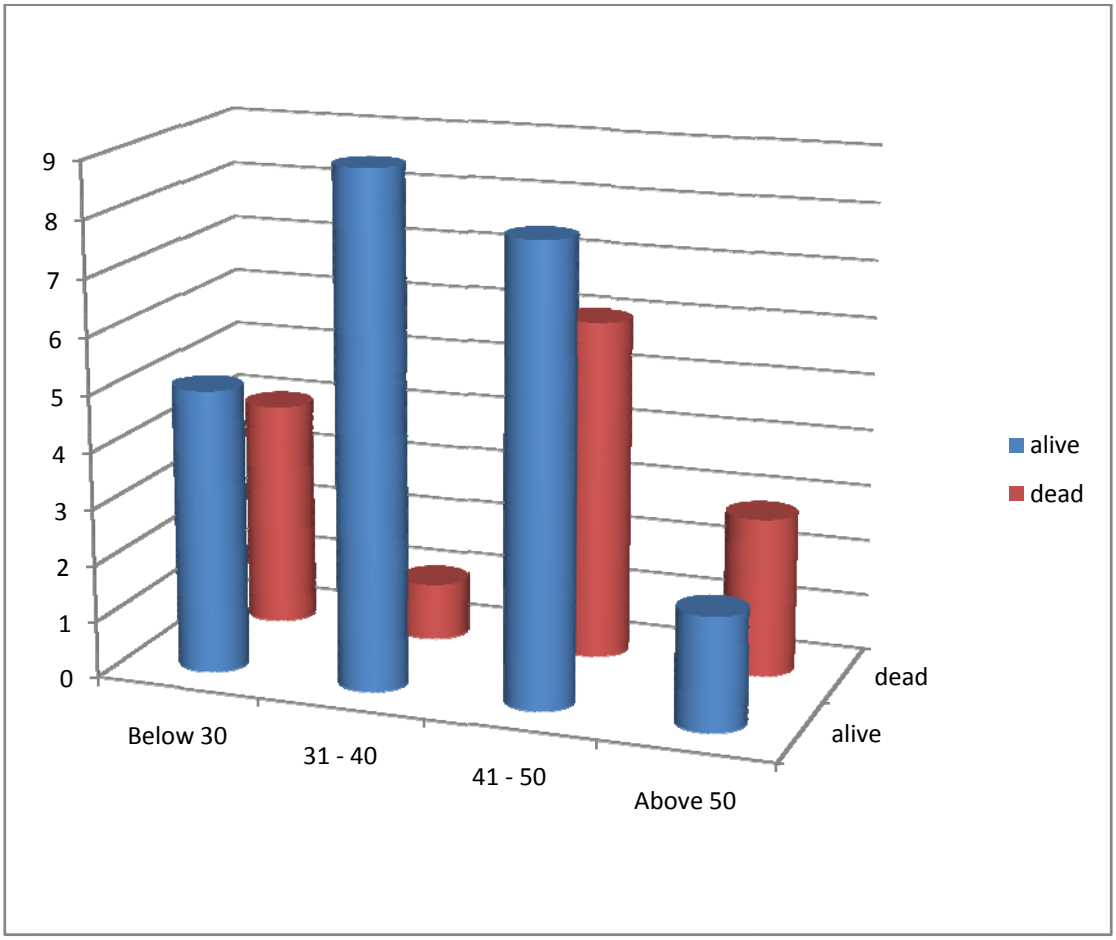
Age in Years and Outcome

Table 17 – Age in years and outcome

Age in years		Outcome		Total	P value
		Alive	Died		
Below 30	Count	5	4	9	0.080
	% within Age in years	55.6%	44.4%	100.0%	
	% within Outcome	20.8%	25.0%	22.5%	
31-40	Count	9	1	10	
	% within Age in years	90.0%	10.0%	100.0%	
	% within Outcome	37.5%	6.3%	25.0%	
41-50	Count	8	6	14	
	% within Age in years	57.1%	42.9%	100.0%	
	% within Outcome	33.3%	37.5%	35.0%	
Above 50	Count	2	5	7	
	% within Age in years	28.6%	71.4%	100.0%	
	% within Outcome	8.3%	31.3%	17.5%	
Total	Count	24	16	40	
	% within Age in years	60.0%	40.0%	100.0%	
	% within Outcome	100.0%	100.0%	100.0%	

In our study, even though 14 out of 40 patients were in the age group between 41- 50, this is not statistically significant. The p value of this correlation is 0.080 which is not statistically significant.

Figure 20 – Comparison between age and outcome



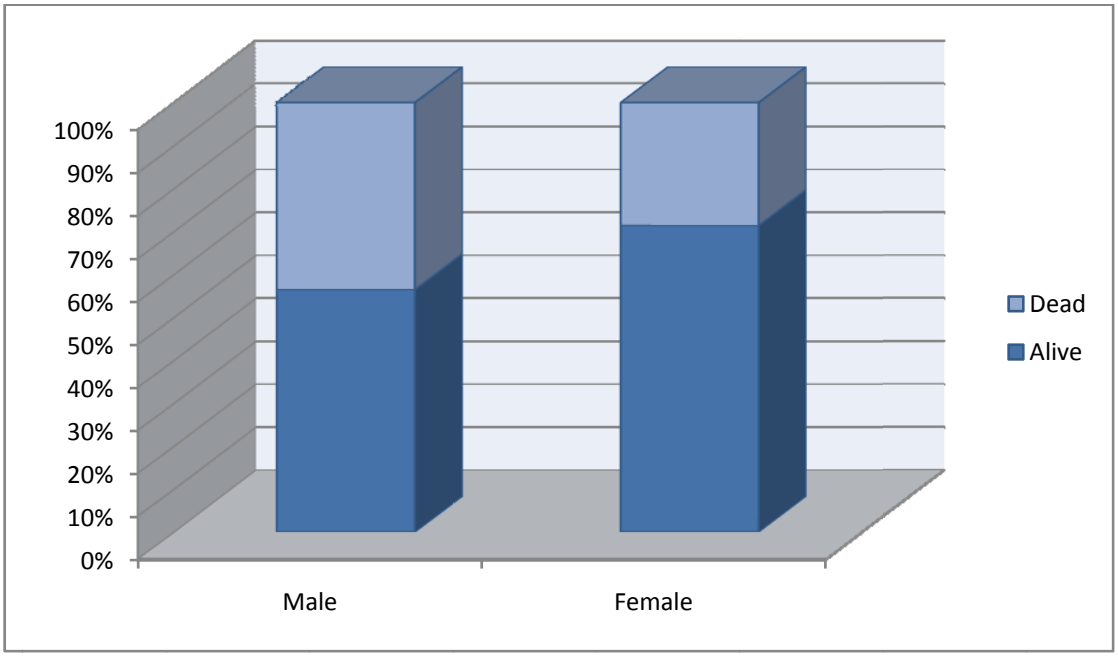
Sex and Outcome

Table 18 – Sex and outcome

Sex		Outcome		Total	P value
		Alive	Died		
Male	Count	13	10	23	.601
	% within Sex	56.5%	43.5%	100.0%	
	% within Outcome	54.2%	62.5%	57.5%	
Female	Count	11	6	17	
	% within Sex	64.7%	35.3%	100.0%	
	% within Outcome	45.8%	37.5%	42.5%	
Total	Count	24	16	40	
	% within Sex	60.0%	40.0%	100.0%	
	% within Outcome	100.0%	100.0%	100.0%	

In our study, even though 23 out of 40 patients were males and 17 were females, this difference was not statistically significant. The p value is 0.601 which is not significant.

Figure 21 – Comparison between sex and outcome



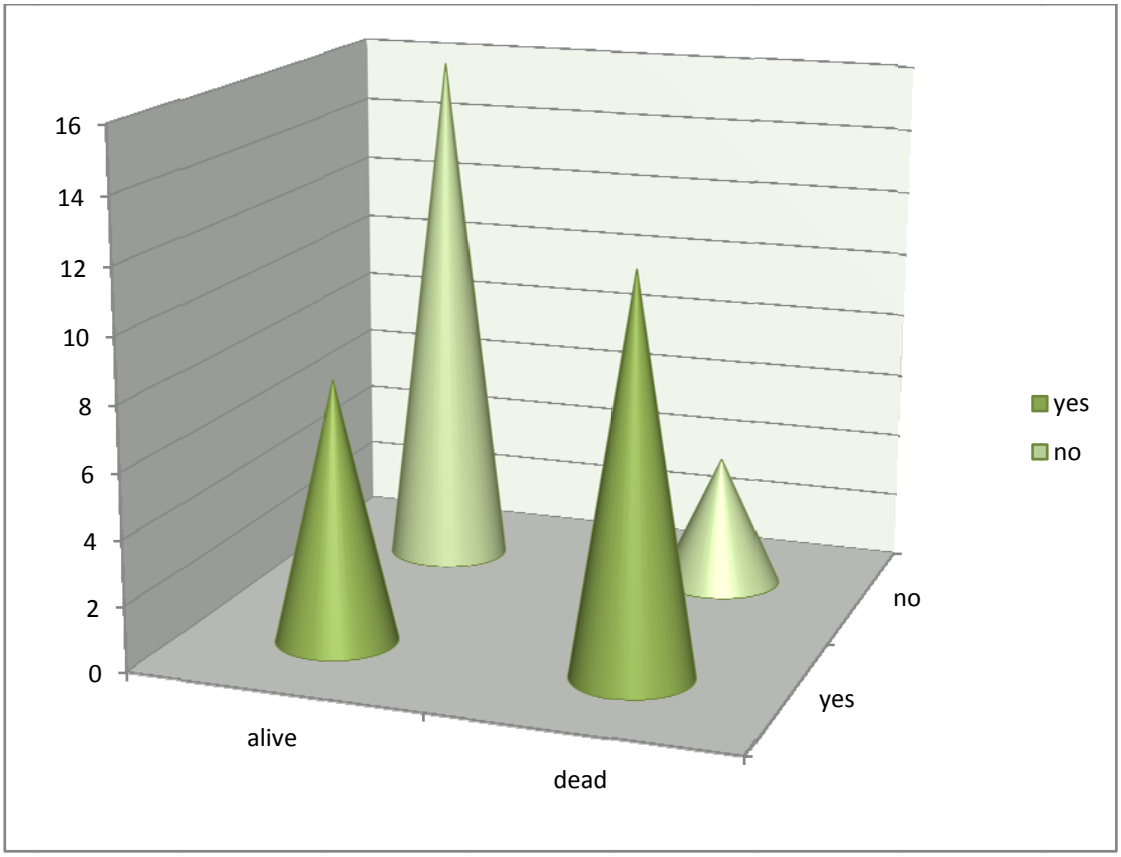
Comparison Between Ventilator Requirement and Outcome

Table 19 – Comparison with ventilator requirement and outcome

VENTILATOR	Frequency	outcome		total	P value
		Alive	Dead		
yes	Count	8	12	20	0.010
	% within outcome	33.3%	75%	50%	
No	Count	16	4	20	
	% within outcome	66.7%	25%	50%	
Total		100%	100%	100%	

In our study, 20 out of 40 patients required ventilator support. This value is statistically significant. The p value is 0.010.

Figure 21 – Comparison between ventilator requirement and outcome



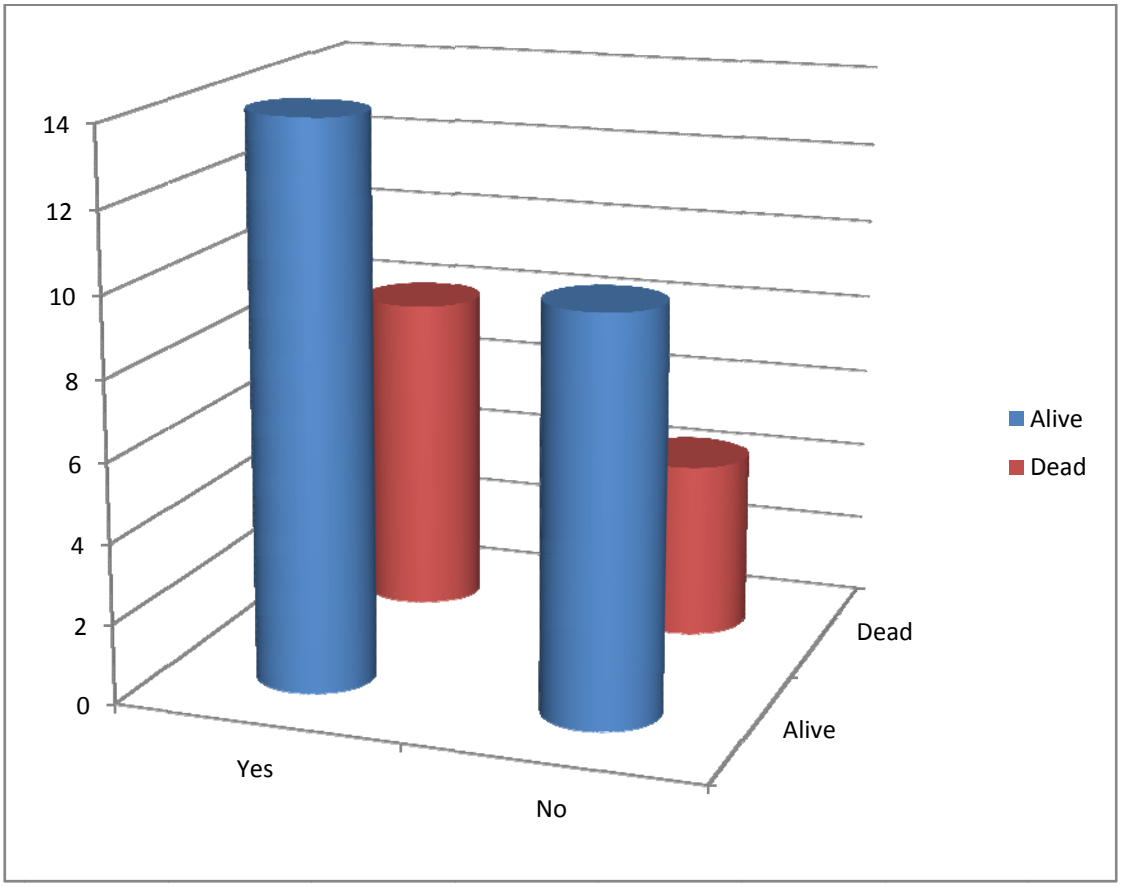
Comparison Between Comorbid Factor (Diabetes Mellitus) and Outcome

Table 20 – Comparison between diabetes mellitus and outcome

Diabetes mellitus	Frequency	outcome		total	P value
		Alive	Dead		
yes	Count	14	8	22	0.604
	% within outcome	58.3	50	55	
No	Count	10	8	18	
	% within outcome	41.7	50	45	
Total		100	100	100	

In our study, 22 patients were having diabetes mellitus and 18 were not having diabetes mellitus. This difference is not statistically significant and the p value is 0.604.

Figure 22 – Comparison between diabetes mellitus and outcome



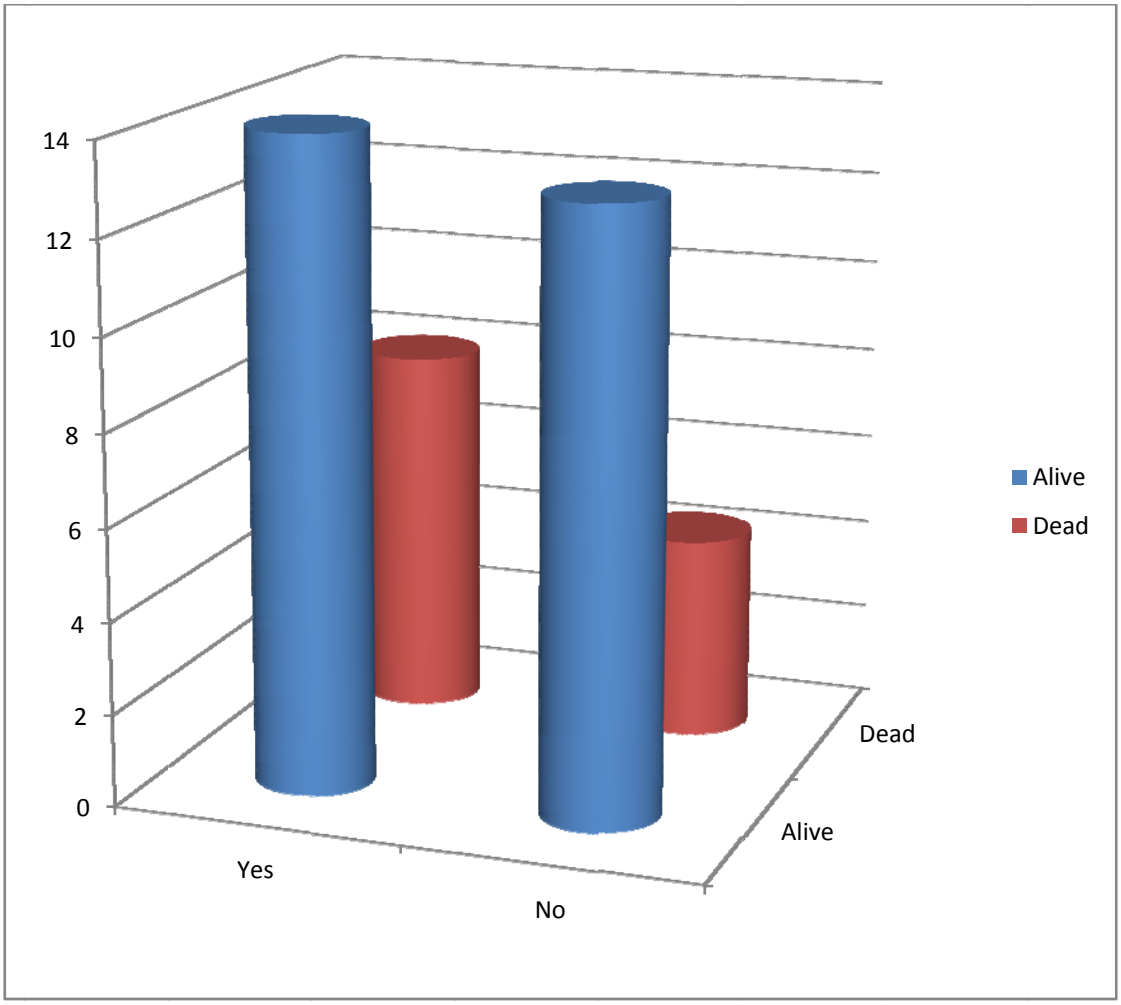
Comparison Between Comorbid Factor (Hypertension) and Outcome

Table 21 – Comparison between hypertension and outcome

Hypertension	Frequency	outcome		total	P value
		Alive	Dead		
yes	Count	11	9	20	0.519
	% within outcome	45.8	56.3	50	
No	Count	13	7	20	
	% within outcome	54.2	43.8	50	
Total		100	100	100	

In our study 20 patients were having hypertension and others were not having hypertension. This difference is not statistically significant. The p value is 0.519.

Figure 23 – Comparison between hypertension and outcome



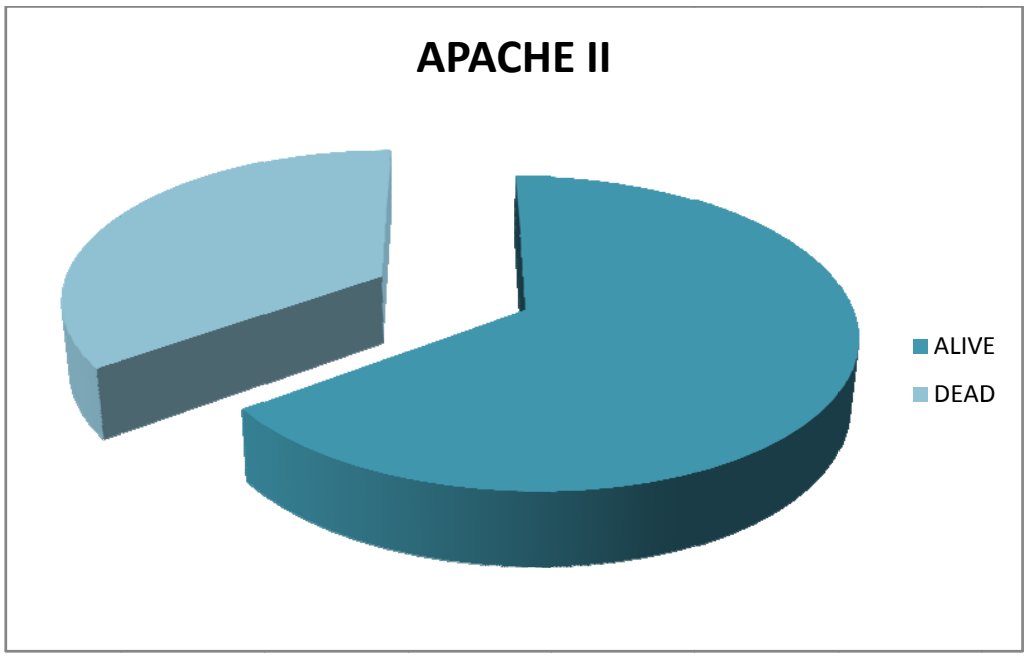
Comparison Between APACHE II and Outcome of the Patients

Table 22 – Comparison between APACHE II and outcome

	Outcome	N	Mean	P value
APACHE II	Alive	24	34.54	<0.001**
	Died	16	43.81	
	Total	40		

In our study, the APACHE II score levels correlated with mortality. The p value for this correlation is <0.001**

Figure 24 – Comparison between APACHE II and outcome



Significance of T3 levels on day 1 and day 7 in Predicting the Outcome of Patients.

Table 23 – Significance of T3 levels in predicting the outcome

	Outcome	N	Mean	P value
T3 - Day 1	Alive	24	48.13	0.087
	Died	16	42.44	
T3 - Day 7	Alive	24	67.33	0.001**
	Died	16	33.88	

In our study, Thyroid function tests were done on day 1 of ICU stay. The p value for T3 levels on day 1 is 0.087 and for day 7 is <0.001**. Based upon the results, the serial measurement of T3 levels will help in predicting the outcome of the patients as an independent factor or in association with APACHE II scores.

Significance of T4 levels on day 1 and day 7 in Predicting the Outcome of Patients.

Table 24– Significance of T4 levels in predicting the outcome

	Outcome	N	Mean	P value
T4 - Day 1	Alive	24	3.9958	0.980
	Died	16	4.0000	
T4 - Day 7	Alive	24	4.9667	0.001**
	Died	16	3.7000	

In our study, Thyroid function tests were done on day 1 of ICU stay. The p value for T4 levels on day 1 is 0.980 and for day 7 is <0.001**. Based upon the results, the serial measurement of T4 levels will help in predicting the outcome of the patients as an independent factor or in association with APACHE II scores.

But the p value of T3 levels on day 1 is 0.087 whereas that of T4 is 0.980. So, when compared to T4, T3 levels will more accurately predict the outcome than T4.

Significance of TSH levels on day 1 and day 7 in Predicting the Outcome of Patients.

Table 25 – Significance of TSH levels in predicting the outcome

	Outcome	N	Mean	P value
TSH - Day 1	Alive	24	.7754	0.085
	Died	16	.4831	
TSH - Day 7	Alive	24	1.2988	0.001**
	Died	16	0.3462	

In our study, Thyroid function tests were done on day 1 of ICU stay. The p value for TSH levels on day 1 is 0.085 and for day 7 is <0.001**. Based upon the results, the serial measurement of TSH levels will help in predicting the outcome of the patients as an independent factor or in association with APACHE II scores.

The significance increases depending on duration of illness.

Correlation Between APACHE II And Thyroid Function Tests On Day 1 In Predicting The Outcome

Table 26 – Correlation between APACHE II and TFT on day 1

		Apache II
T3 - Day 1	P value	.002
	N	40
T4 - Day 1	P value	.551
	N	40
TSH - Day 1	P value	.216
	N	40

In our study, APACHE II score which is calculated within 24 hours of ICU admission is compared with thyroid function tests which is taken on day1. The results obtained with this comparison is that on day 1 levels of T3 significantly correlated with APACHE II scores whereas T4 and TSH levels are not statistically significant.

Correlation Between APACHE II And Thyroid Function Tests On Day 7 In Predicting The Outcome

Table 27 – Correlation between APACHE II and TFT on day 7

		Apache II
T3 - Day 7	P value	.001**
	N	40
T4 - Day 7	P value	.010
	N	40
TSH - Day 7	P value	.013
	N	40

In our study, APACHE II score is also compared with thyroid function test which is taken on day 7. The results obtained with this comparison is that on day 7 levels of T3, T4 and TSH significantly correlated with APACHE II scores in predicting the outcome of the patients. The significance of T3 is higher when compared to T4 and TSH.

DISCUSSION

DISCUSSION

This study was conducted in the patients admitted in ICU irrespective of the diagnosis. The study group size was 40. Patients included in the study were closely monitored and thyroid function tests were taken on day 1 and day 7 as explained in methodology. All the patients are followed till the outcome which was either recovery and discharge or death of the patient. Outcome analysis was done in comparison with whether thyroid function tests were able to predict the outcome of the patients independently. The significance is also assessed by comparison of thyroid hormone levels with APACHE II scores. Following were the main observations of the study.

AGE AND SEX DISTRIBUTION:

Out of 40 patients, maximum number of patients were observed in the age group of 41 – 50 years with the percentage of 35% as observed in the frequency distribution table. Out of 40 patients, 23 (57.5%) patients were male and 17 (42.5%) patients were female.

Chi square tests were applied to these values to observe whether age and sex distribution affects the outcome of the study. The observed p values for age distribution are 0.080 and for sex distribution is 0.601. Both the values are not statistically significant. So age and sex distribution did not affect the outcome of the study.

COMORBID FACTORS:

Out of 40 patients, 22 patients were having diabetes mellitus and 18 were not having diabetes mellitus. 20 patients were having hypertension and 20 patients were without hypertension. Statistical tests were also applied to these co morbid factors to observe whether they affect the outcome of the study. The p values observed for diabetes mellitus was 0.604 and for hypertension was 0.519. Both these values are not statistically significant and they did not affect the outcome of the study.

VENTILATOR AND OUTCOME:

In the study group population, 20 patients required ventilator support. Out of the 20 patients, 12 patients expired and 8 of them survived. Out of 20 patients not requiring ventilator support 16 of them survived and 4 patients expired. Chi square tests were applied to observe whether the requirement of ventilator significantly affect the outcome of the study. The observed p value was 0.010, this was statistically significant in affecting the outcome of the study.

APACHE II SCORE AND OUTCOME:

APACHE II scores were calculated for all the 40 patients to assess whether thyroid function tests could independently predict the outcome of

the patients. Statistical tests were applied to APACHE II scores separately to observe whether the scores are statistically significant.

The observed p value for APACHE II score predicting the mortality separately was <0.001**. This result was statistically significant. As documented in previous studies, in this study also APACHE II score affects the outcome of the patients.

THYROID PROFILE AND OUTCOME:

Thyroid profile was taken from all subjects on day 1 and day 7 as per inclusion and exclusion criteria. T3, T4 and TSH values are separately subjected to statistical analysis and also they are compared with APACHE II score in predicting the outcome.

As for day 1, the observed p values for T3 in predicting the outcome was 0.087, for T4 was 0.980 and for TSH was 0.085. These values are not statistically significant. The p values, seen on day 7 for T3 in predicting the outcome was 0.001, T4 was 0.001 and for TSH was 0.001. All these values are statistically significant in predicting the outcome of the patient as an independent factor in predicting the outcome of the patient.

Again the thyroid profile was compared with APACHE II scores in predicting the outcome. On day 1, the observed p values for the correlation for T3 was 0.002, T4 was 0.551 and for TSH was 0.216. T3 values on day 1

correlated with APACHE II scores in predicting the outcome based on statistical analysis. Wang et al in 2012 done a study on relation between thyroid function and ICU mortality also showed that low T3 can predict the mortality of the patients.

Thyroid function tests obtained on day 7 were again compared with APACHE II scores in predicting the outcome. Based upon statistical analysis the observed p values were 0.001 for T3, 0.010 for T4 and 0.013 for TSH. All these values are statistically significant.

Thyroid profile measured serially in ICU patients can independently predict the outcome of the patients.

CONCLUSION

CONCLUSION

Following results were concluded from the study:

1) Thyroid profile can be used in predicting the morality in ICU patients.
2) Serial monitoring of thyroid profile will increase the sensitivity in predicting the outcome.
3) Outcomes assessed by thyroid profile are comparable with that of APACHE II scores.
4) Thyroid profile can be used as an independent factor in predicting the outcome of the patients.
5) Thyroid profile can also increase the sensitivity of APACHE II score in predicting the outcome.

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ANNEXURES

"RELATIONSHIP BETWEEN THYROID FUNCTION AND ICU MORTALITY (SICK EUTHYROID SYNDROME)"

PROFORMA

Name: Age/Sex:

Address: Occupation:

SYMPTOMS:

PAST HISTORY:

THYROID ILLNESS	
HYPERTENSION	
DIABETES MELLITUS	
INTAKE OF ANY OTHER MEDICATIONS	
USAGE OF IODINE CONTRAST AGENTS	

PERSONAL HISTORY:

SMOKING

ALCOHOL

GENERAL EXAMINATION:

GCS	

VITAL SIGNS:

PR-

BP-

RR-

SYSTEMIC EXAMINATION:

CVS:

RS:

ABDOMEN:

CNS:

THYROID EXAMINATION:

INVESTIGATIONS:

COMPLETE HEMOGRAM

RFT/ELECTROLYTES

LFT

ECG

APACHE II SCORE

THYROID HORMONE ASSAY

DAY 1

DAY 7

OUTCOME

ASSESSMENT :

S.No	Duration of stay	Thyroid assay day1	Thyroid assay day7	APACHE II	Ventilatory support(if)		Outcome	
					✓	☒	Recovery	Death

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.M.M.Arun Shiva Raman
Postgraduate M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.M.M.Arun Shiva Raman,

The Institutional Ethics Committee has considered your request and approved your study titled **"Relationship between thyroid function and ICU mortality (Sick Euthyroid syndrome)" No.27042015.**

The following members of Ethics Committee were present in the meeting held on 07.04.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.S.Baby Vasumathi, Director, Inst. Of O&G, MMC	: Member
7. Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
10. Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
11. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

INFORMATION SHEET

We are conducting a study on **"RELATIONSHIP BETWEEN THYROID FUNCTION AND ICU MORTALITY (SICK EUTHYROID SYNDROME)"** among patients admitted in ICU in Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the levels of thyroid hormone in acutely ill patients admitted in ICU and the correlation between their levels in predicting the mortality in patients who are admitted for more than a week.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the investigator Signature of the participant

Date: Signature of the caregiver

Place:

PATIENT CONSENT FORM

Study Detail : "RELATIONSHIP BETWEEN THYROID FUNCTION AND ICU MORTALITY (SICK EUTHYROID SYNDROME)"

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

e) I hereby consent to participate in this study. ☐

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ☐

Signature/thumb impression

Signature of the investigator

Care giver's signature

Study investigator's name

Dr. M. M. ARUN SHIVA RAMAN

ஆராய்ச்சிஒப்புதல்கடிதம்

ஆராய்ச்சி தலைப்பு:

அதிதீவிர சிகிச்சைப்பிரிவில் அனுமதிக்கப்பட்டுள்ள நோயாளிகளுக்கு நோயினால் வரும் தைராய்டுஹார்மோன் மாற்றங்களையும் அதனால் வரும் விளைவுகளையும் கண்டறிவதைபற்றிய ஆராய்ச்சி.

பெயர்: தேதி:

வயது: உள்நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

அதிதீவிர சிகிச்சைப்பிரிவில் அனுமதிக்கப்பட்டுள்ள நோயாளிகளுக்கு நோயினால் வரும் தைராய்டுஹார்மோன் மாற்றங்களைகண்டறிய மேற்கொள்ளப்படும் பரிசோதனைகளைப் பற்றியும் ஆராய்ச்சியாளர் கூற முழுவதும் விளங்கப்பெற்றேன்.

மேற்கொண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

கையொப்பம்

“RELATIONSHIP BETWEEN THYROID FUNCTION AND ICU MORTALITY (SICK EUTHYROID SYNDROME)”

MASTER CHART

S.NO	AGE	SEX	VENTILATOR	DIABETES MELLITUS	HYPERTENSION	APACHE II	THYROID PROFILE						DIAGNOSIS	OUTCOME
							DAY 1			DAY 7				
							T3	T4	TSH	T3	T4	TSH		
1	32	F	Y	Y	Y	32	34	3.5	0.84	40	3.8	2.1	SCRUB TYPHUS/ARDS	A
2	38	F	N	Y	Y	38	36	3.6	0.49	41	4	0.55	SIRS-INFECTIVE	A
3	39	M	N	Y	N	33	48	4	0.31	57	4.3	0.32	DIABETIC FOOT/SEPSIS	A
4	58	M	Y	N	Y	42	42	3.8	0.3	35	3.6	0.34	CAD/P EDEMA	D
5	55	M	Y	Y	Y	47	37	3.5	0.68	48	3.9	1.54	ACUTE CVA	A
6	32	M	N	N	N	35	55	4.6	0.88	63	5.2	2.1	HANGING	A
7	48	M	Y	Y	Y	46	32	2.8	0.27	28	2.6	0.24	UROSEPSIS/SEPTIC SHOCK	D
8	28	F	N	Y	N	44	28	3.3	0.26	39	3.9	0.73	T1DM/DKA	A
9	22	M	Y	N	N	43	31	3	1.66	27	3.4	0.9	SNAKE BITE	D
10	43	F	N	Y	N	46	35	3.7	0.21	30	3.3	0.18	EMPHYSEMATOUS PYELONEPHRITIS	D
11	36	M	Y	Y	Y	38	58	4.2	0.53	67	4.6	0.72	OPC POISONING	A
12	42	M	Y	N	Y	37	53	4.1	0.34	45	4	0.32	PONTINE HEMORRHAGE	D
13	45	F	N	Y	N	40	48	4.3	1.5	68	7	0.96	CAD/ACS	A
14	36	F	Y	Y	Y	41	43	4.7	0.36	61	6.9	1	PNEUMONIA	A
15	54	F	Y	Y	Y	45	44	3.9	0.27	37	3.6	0.23	MENINGITIS	D

16	48	M	N	Y	N	37	53	4.3	0.86	68	5.2	1.56	CAD/ACS/AWMI	A
17	43	M	N	N	N	35	63	4.9	1.23	79	5.7	2.3	SVT	A
18	26	M	Y	Y	N	45	52	4.2	0.29	36	3.8	0.15	SEPSIS/ARDS	D
19	49	F	Y	N	N	38	38	3.1	0.36	51	4.5	0.86	SCORPION STING/P EDEMA	A
20	42	F	N	Y	Y	46	48	4.1	0.86	32	3.9	0.25	CAD/ACS/VT	D
21	60	F	N	N	Y	47	43	4.2	0.18	27	3.8	0.15	SAH	D
22	23	M	Y	N	N	33	72	4.6	0.82	102	6	2.4	OPC POISONING	A
23	32	M	Y	Y	N	42	44	3.9	0.23	33	3.5	0.21	MUCORMYCOSIS-MAXILLARY SINUS	D
24	58	M	Y	Y	Y	35	38	3.6	0.37	51	4.8	0.41	CAD/ACS/NSTEMI	A
25	49	M	Y	N	Y	48	36	3.9	0.34	28	3.3	0.22	CAD/CARDIOGENIC SHOCK	D
26	26	F	N	Y	N	34	62	4.5	0.6	89	8.1	2.1	UROSEPSIS/DKA	A
27	46	M	N	N	Y	37	42	3.6	1.2	91	3.7	2.3	ACUTE CVA	A
28	20	F	Y	Y	N	41	55	4.5	0.41	32	4.1	0.32	SEPSIS/ARDS	D
29	46	M	N	N	Y	35	38	4.2	2.8	62	5.1	3.1	HANGING/PULMONARY EDEMA	A
30	38	F	N	N	Y	26	51	4.1	0.39	73	4.5	0.51	SNAKE BITE/NEUROTOXIC	A
31	43	M	Y	Y	Y	45	43	4.7	0.53	37	4.3	0.46	CAD/DCM/C SHOCK	D
32	32	M	N	Y	N	28	55	3.9	0.36	74	5.4	0.62	OLEANDER SEED POISONING	A
33	65	M	Y	N	Y	44	34	4.3	0.33	33	4.4	0.26	ACUTE CVA/ICH	D
34	29	F	N	N	N	25	54	4.1	0.35	81	5.1	0.56	RAT KILLER PASTE POISONING	A
35	41	M	N	Y	Y	27	61	4.3	1.56	64	5.2	1.77	COMPLICATED MALARIA	A
36	33	F	N	N	N	31	48	3.8	0.92	85	4.6	1.1	COMPLICATED MALARIA	A
37	29	F	Y	N	N	43	54	4.3	1.13	51	4.5	1.15	SNAKE BITE	D
38	25	M	N	Y	N	29	38	3.1	0.61	57	3.5	1.21	T1DM/DKA	A
39	49	F	Y	N	Y	31	55	4.1	0.33	105	4.2	0.35	PNEUMONIA	A
40	56	M	N	N	N	41	33	4.6	0.38	31	3.1	0.16	MENINGITIS	D

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Submitted in partial fulfillment of

the requirements for

M.D. DEGREE EXAMINATION

BRANCH I - GENERAL MEDICINE

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

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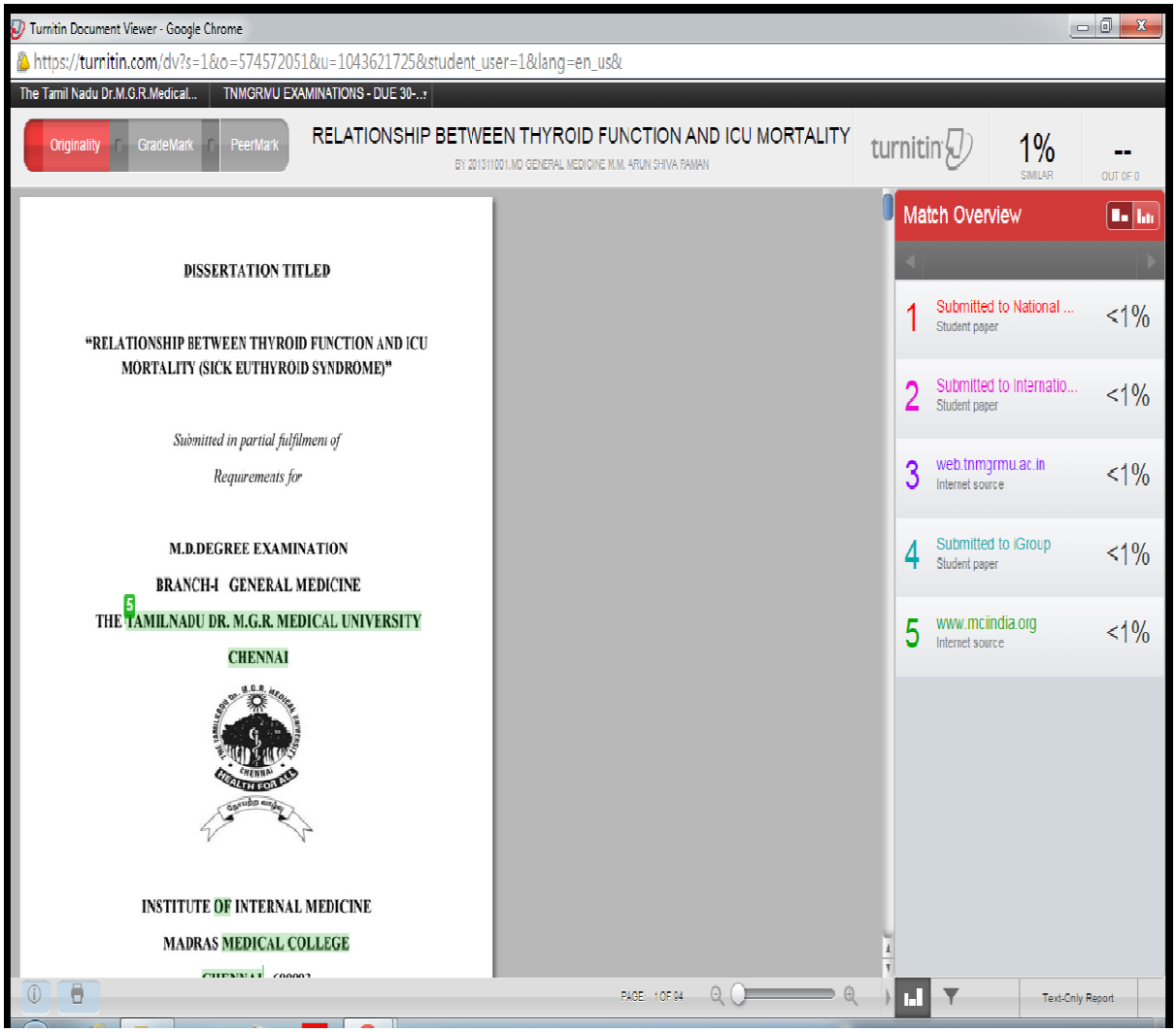
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